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Effect of Testosterone Propionate on Losses Incident to Inadequate Dietary Intake[1,2]

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IT IS KNOWN that the ratio of potassium to nitrogen lost from the body during short periods of starvation with or without marked dehydration may exceed the ratio of potassium to nitrogen in normal muscle tissue (5, 6, 10, 12, 13, 16, 32). It has also been observed that the administration of testosterone to subjects receiving an adequate diet may at first lead to a ratio of potassium to nitrogen retained in the body greater than that which pertains in normal muscle tissue (28, 29). In such subjects the serum potassium may fall to extremely low levels (7, 28, 29). The administration of testosterone to an obese man during a period of submaintenance diet and weight loss resulted in a diminution in the urinary nitrogen output and an increase in the urinary excretion of organic acids (23). This observation suggests that testosterone diminishes the rate of utilization of protein or muscle tissue and necessitates an increase in the oxidation of fat to meet the energy requirements.

The availability of certain experimental data (10, 11) which could serve as controls led us to inquire further into the effect of testosterone on the metabolism of the inadequately nourished subject and its possible therapeutic use in preventing protein loss

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incident to the unavoidable starvation suffered by many patients. To this end supplementary experiments were carried out to determine in some detail the effects of intramuscularly administered testosterone propionate upon the losses of body substances by normal human subjects during six day periods of absolute or partial fasting.

METHODS OF STUDY

Four healthy young men from C.P.S. Camp No. 115 volunteered to be the subjects for these investigations. Their normal body weights were approximately as follows: *W.H.*, 75; *R.E.*, 67; *E.B.*, 70; and *P.J.*, 66 kilograms, respectively. The daily intake over the six day periods without testosterone and the six day periods with testosterone was for *W.H.* only 1000 cc. of water daily; for *R.E.*, 1000 cc. of water plus 50 gm. of glucose; for *E.B.*, 1200 cc. of water, 4.5 gm. of sodium chloride and 100 gm. of glucose; and for *P.J.*, 1000 cc. of water and 300 gm. of glucose. The important variable other than testosterone which concerns us in this study was the quantity of glucose. The variations in water and sodium chloride were incident to other studies.

The first time each subject had received his particular dietary regime for the six day period, he received no testosterone (10, 11). The second time, for eight days preceding the experimental period and for the six day period of the restricted regime he was given 25 milligrams of testosterone propionate intramuscularly daily. The two experimental periods were separated by a recovery period of at least one month.

During the experimental periods, the urine was collected in 24 hour lots. No stools were passed. In addition fasting blood was withdrawn for certain measurements on the morning of the 3rd and 6th days. Most of the methods of analysis are listed in a previous publication (28). In addition the following methods were also used: amino-acid nitrogen (31), organic acids (22),[3] acetone bodies (22),[4] milliosmols (21).

[3] Page 647.
[4] Pages 626–629.

RESULTS

Considerable experience with metabolic studies over six day periods of starvation or very inadequate caloric intake (5, 10–12) has shown that the renal excretion of various substances over the last four days of the period reflects with great consistency the effect of the experimental regime on the individual's metabolism. On the other hand, the urinary excretion of the first two days reflects the foreperiod regime and condition of the subject as well as the experimental regime. Accordingly, in the presentation of these data emphasis has been placed on those pertaining to the last four days.

The data of figures 1 to 4 (left hand portions) show that during the last four days of periods of testosterone propionate administration all subjects excreted less total nitrogen (average decrease, 33 mg. per kg. per day) than they did during control periods. This decrease in total nitrogen excretion was due to a diminution in the urea output (average decrease, 34 mg. per kg. per day). The effect of the varying amounts of glucose per se upon the elimination of total nitrogen is shown in figure 5. The largest excretion values per kg. of body weight were obtained for subject *W.H.*, who received nothing but water. The administration of 50 grams of glucose resulted in a moderate decrease, while the administration of 100 grams of glucose prompted as great a decrease in the total urinary nitrogen as did 300 grams of glucose. The output of urea and of total nitrogen tended to diminish from the 3rd to the 6th day of the experimental periods both with and without testosterone.

Figure 6 reveals that testosterone propionate also tended to cause a slight increase in the preformed creatinine excretion, and a decrease in the output of creatine. The increase in preformed creatinine was on the average 1.2 milligrams per kilogram per day. This value is approximately six per cent of the value for the average excretion of preformed creatinine during the control periods. On the other hand, the decrease in creatine averaged 1.6 milligrams per kilogram per day, a value equal to 37 per cent of the average

daily creatine output during the control periods. The testosterone therapy did not influence the urinary excretion of ammonia or amino acids; the average elimination of

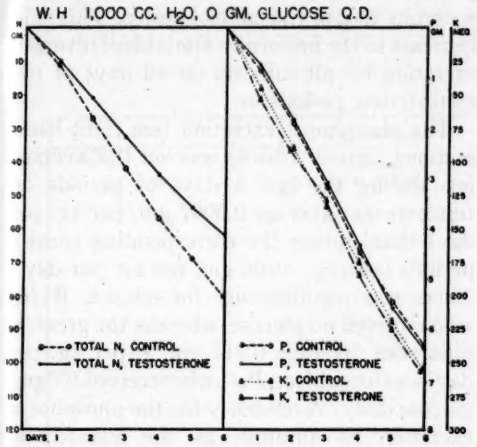

FIG. 1. Effect of testosterone propionate therapy (25 mg. per day i.m.) on the daily urinary total nitrogen (left hand section), potassium and phosphorus losses (right hand section) of subject *W.H.* during six day periods of absolute fasting. The meaning of each curve is given by the legends near the bottom of the figure. The scale for total nitrogen is given along the left hand ordinate while those for potassium and phosphorus are set forth along the right hand ordinate. The points defining the lines were determined by adding the excretion value of that day to the value for the preceding day.

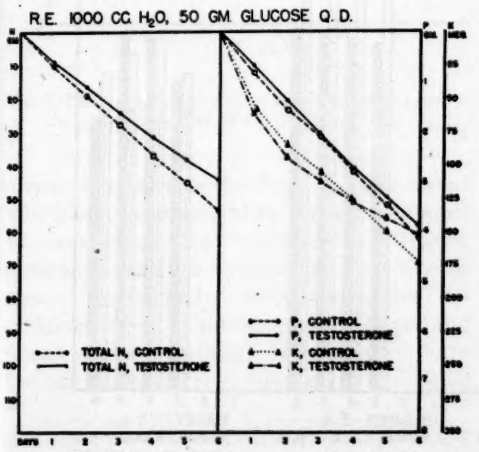

FIG. 2. Effect of testosterone propionate therapy (25 mg. per day i.m.) on the urinary total nitrogen, potassium and phosphorus losses of subject *R.E.*, who received 50 grams of glucose daily. The design of this figure corresponds to that of figure 1.

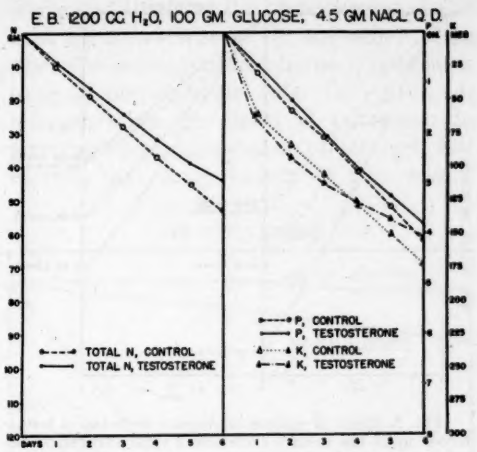

FIG. 3. Effect of testosterone propionate therapy (25 mg. per day i.m.) on the urinary total nitrogen, potassium and phosphorus losses of subject *E.B.* who received 100 grams of glucose daily. The design of this figure corresponds to that of figures 1 and 2.

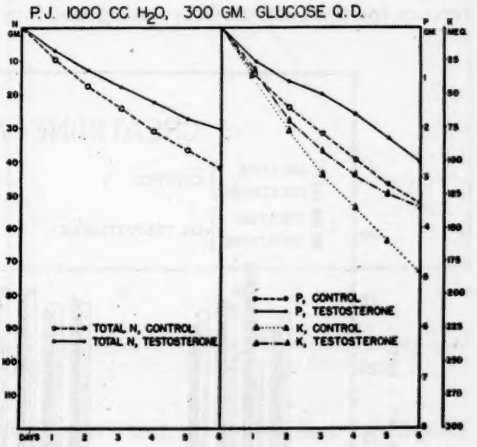

FIG. 4. Effect of testosterone propionate therapy (25 mg. per day i.m.) on the urinary total nitrogen, potassium and phosphorus losses of subject *P.J.* who received 300 grams of glucose daily. The design of this figure corresponds to that of figures 1 to 3.

amino acids by the subjects during both the control and testosterone periods being approximately 1.0 milligram per kilogram per day.

With the exception of *W.H.* (0 gm. glucose), the elimination of potassium was appreciably less during periods on testosterone than during control periods (right

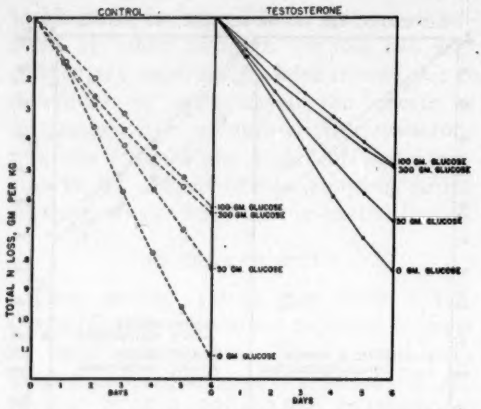

FIG. 5. Effect of various inadequate diets and of testosterone upon the urinary excretion of total nitrogen by the subjects of Figures 1 (*W.H.*, 0 grams glucose), 2 (*R.E.*, 50 grams of glucose), 3 (*E.B.*, 100 grams glucose) and 4 (*P.J.*, 300 grams glucose). The left hand portion of the figure represents control periods; the right hand portion represents periods on testosterone.

hand sections, figures 1 to 4). The average difference for the four subjects during last four days of the periods was 0.09 milliequivalent per kilogram per day. However, for each subject the potassium excretion during the testosterone period exceeded or equalled the potassium excretion on at least one corresponding day of the control period. This is in contrast to the uniformly diminished nitrogen excretion for all subjests on all days of the testosterone periods.

The phosphorus excretion (see right hand sections, figures 1 to 4) was on the average less during the last 4 days of periods on testosterone (average 0.0097 gm. per kg. per day) than during the corresponding control periods (average .0106 gm. per kg. per day). There was no difference for subject, *W.H.*, who received no glucose, whereas the greatest difference (average 0.017 gm. P per kg. per day) was for subject, *P.J.*, who received 300 gm. glucose daily. A tendency for the phosphorus excretion to diminish as the quantity of glucose in the diet was increased was also noted.

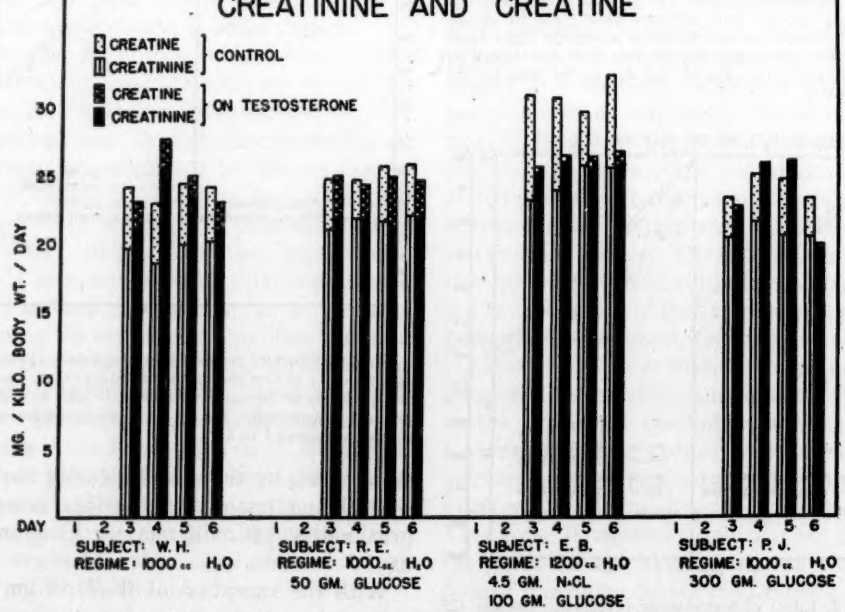

FIG. 6. Effect of testosterone propionate upon urinary preformed creatinine and creatine excretion during days three to six of six day periods of inadequate dietary intake. The subjects and dietary regimes are the same as those of figure 1. A legend in the top left hand quadrant gives the meaning of the columns. A scale in milligrams of creatinine or creatine (both expressed as creatinine) excreted per kilogram of body weight per day is given along the left hand ordinate.

Figures 1 to 4 also permit a consideration of the ratios of potassium to nitrogen and of phosphorus to nitrogen excreted during the control and testosterone periods. It will be noted that the scales for nitrogen, potassium and phosphorus are so designed that a horizontal line drawn across the figures at any level intersects the three scales at values which bear approximately the same relation to each other that pertain for nitrogen, potassium and phosphorus in true muscle tissue.[5] Accordingly, when the curves describing urinary nitrogen, potassium and phosphorus excretions, respectively, have the same slope, these substances are being eliminated in about the same proportions as exist in muscle tissue. On the other hand, when the curves for phosphorus or potassium have a steeper slope than the curve for nitrogen, then the ratio of potassium to nitrogen or of phosphorus to nitrogen lost exceeds that characteristic of true muscle tissue. Such high ratios are evident in figures 1 to 4 and especially in figure 1 (*W.H.*, 0 gm. glucose). In this figure it can also be seen that while testosterone diminished the nitrogen output, it had essentially no effect on the phosphorus or potassium output. Accordingly testosterone therapy resulted in higher P/N and K/N ratios in this subject. However, for the subjects of Figures 2 to 4 who received varying amounts of glucose, testosterone treatment had only a slight and irregular tendency to increase the P/N and K/N ratios. On the other hand, it is of interest that while these three subjects ex-

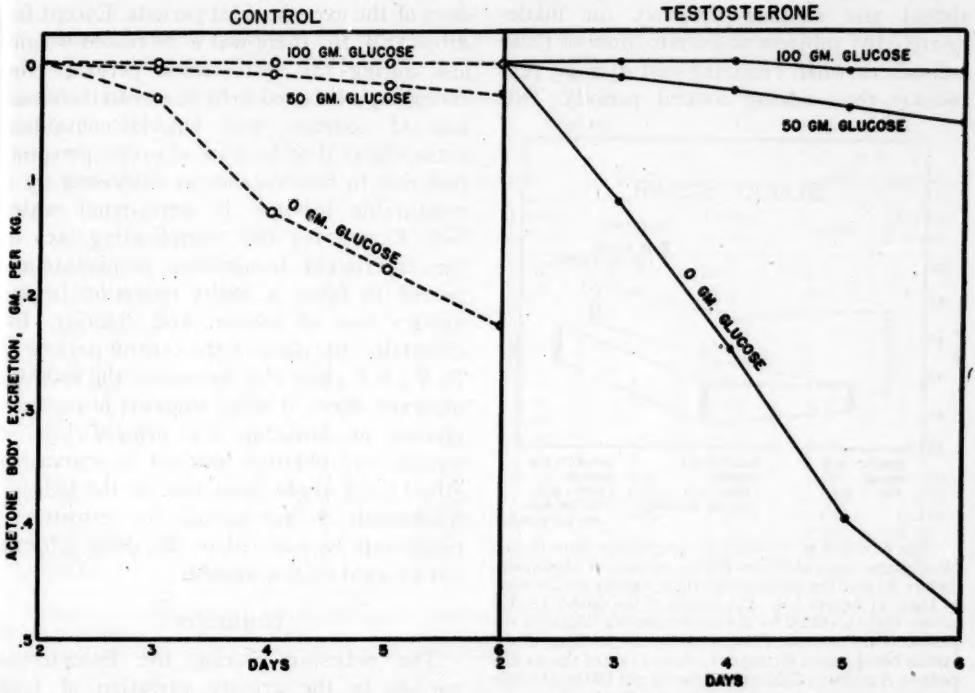

FIG. 7. Effect of testosterone and of diet upon the urinary output of acetone bodies. The subjects are the same as those of the preceding figures (*W.H.*, 0 grams glucose, fig. 1; *R.E.*, 50 gm. glucose, fig. 2; *E.B.*, 100 gm. glucose, fig. 3).

[5] As discussed previously, in true muscle there are approximately 2.86 milliequivalents of potassium per gram of nitrogen (28). The ratio of phosphorus to nitrogen in muscle is approximately 0.067 grams P to 1 gram N (24). In Figures 1 to 4 the scales are drawn for convenience in plotting in such a manner that multiples of 2.5 milliequivalents of potassium, 0.067 grams of phosphorus and 1 gram of nitrogen fall on horizontal lines.

creted potassium as rapidly during the first two days of the testosterone periods as they did during the first two days of the control periods, they tended to excrete less during the last four days while receiving testosterone.

The urinary excretion of acetone bodies is shown in figure 7. Here is observed a consistent and striking tendency for inadequately fed subjects to excrete more of these substances when receiving testosterone propionate than during control periods. This

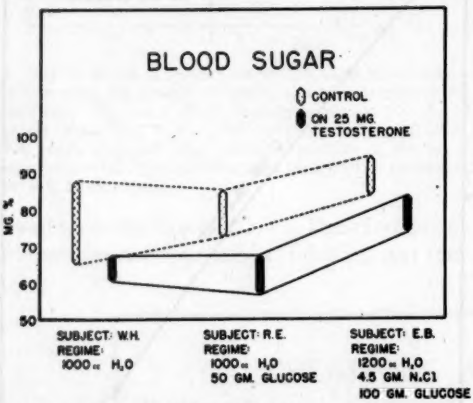

FIG. 8. Effect of testosterone propionate upon fasting blood sugar concentrations during periods of inadequate dietary intake. The subjects and their regimes are the same as those of figures 1–6. The length of the double headed arrows (light speckled for the control periods; black for the periods of testosterone therapy) indicates the range of the fasting blood sugars during days three to six of the six day periods. A scale in milligrams of glucose per 100 cc. of whole blood is presented along the left hand ordinate.

tendency was most marked in the subject who received no glucose and was less striking, the larger the glucose intake. The curves representing *P.J.* (300 gm. glucose) are not shown because he excreted essentially no acetone bodies during either regime.

Figure 8 presents the range of fasting blood sugar concentrations of the subjects who received 0, 50, and 100 gm. of glucose per day, respectively. It is seen that these blood sugar values were consistently higher during control periods than during testosterone periods.

The administration of testosterone propionate did not induce any significant changes in the concentrations of serum sodium, chloride, phosphorus or protein. The serum potassium varied but little.

Table 1 summarizes much of the foregoing information and presents certain other data not previously mentioned; namely, body weight loss and urinary sodium, chloride, organic acids, and milliosmol excretion. The values given are averages for the last four days of the experimental periods. Except for subject, *W.H.*, there was a decreased weight loss during the testosterone periods. The exception is believed to be due to an increased loss of sodium- and chloride-containing extracellular fluid because of excess perspiration due to hot weather as evidenced by a measurable increase in extra-renal water loss. Except for this complicating fact in this experiment, testosterone propionate appeared to favor a slight reduction in the urinary loss of sodium and chloride. Incidentally, the data of the control periods of *W.H.*, *R.E.*, and *P.J.* exemplify the recently observed effect of small amounts of ingested glucose on reducing the urinary loss of sodium and chloride incident to starvation (10, 11). A slight reduction in the urinary milliosmols during periods on testosterone propionate were noted in the three subjects not affected by hot weather.

COMMENTS

The reduction during the testosterone periods in the urinary excretion of total milliosmols, nitrogen, potassium and phosphorus by these fasting or partially fasting subjects is in general agreement with the increased retention of these substances that is known to result from the administration of testosterone propionate to individuals receiving an adequate diet (1, 8, 14, 15, 17, 28–30). The increased excretion of preformed creatinine and the decreased excretion of creatine have already been noted and commented on by others (8, 14, 15, 28).

The increase in acetone body excretion and hence in organic acid output in the testosterone periods confirms the observation on the obese subject (23) receiving an inadequate caloric intake referred to in the introduction. The tendency towards a lower-

ing in fasting blood sugar values in association with the increased urinary output of acetone bodies and decreased urinary urea suggests diminished gluconeogenesis during the testosterone periods. The tendency of testosterone to cause an increase in the ratios of potassium to nitrogen and of phosphorus to nitrogen in the urine of the present subjects is in contrast to the decrease in the potassium to nitrogen ratio that may follow its administration to adequately fed subjects (28, 29). This increased urinary excretion of potassium and phosphorus relative to nitrogen in the testosterone periods may well reflect the liberation of glycogen-bound potassium and phosphorus as the result of an accelerated or increased glycogenolysis (9).

The foregoing observations, taken together, suggest that testosterone therapy alters the relative rates at which protein, fat and carbohydrate are catabolized by subjects receiving an inadequate caloric intake. They support the thesis that testosterone inhibits the utilization of protein or muscle tissue as a source of required calories and that there is a compensatory increase in the catabolism of fat (2).

In these respects Benedict's observations on the fasting subject, *L.*, may be pertinent (3). Figure 9 describes the calculated sources of energy expended by *L.* during the first six days of his 30 day fast. During the first three days, approximately 13 per cent of the calories were derived from carbohydrate and 13 per cent from protein. Fat provided the remainder of the caloric requirements. However, by the 4th day, the carbohydrate stores (glycogen) became depleted, so that only 1 or 2 per cent of calories were provided by the oxidation of carbohydrate, while about 19 per cent were obtained from protein oxidation and 80 per cent from fat. As the calories provided by carbohydrate diminished, the calories provided by the combustion of protein tended to increase. A slight decrease in the caloric expenditure is also noted.

The total urinary nitrogen excretion per kilogram per day of Benedict's subject, *L.*, and of subject *W.H.* of the present studies

TABLE I. AVERAGE LOSSES OF BODY WEIGHT AND OF VARIOUS URINARY CONSTITUENTS DURING DAYS THREE TO SIX INCLUSIVE, OF CONTROL PERIODS AND OF PERIODS ON TESTOSTERONE PROPIONATE. RESULTS EXPRESSED AS UNITS PER KILOGRAM PER DAY.

Substance lost	Subject							
	W.H. Fasting		*R.E.* 50 gm. glucose		*E.B.* 100 gm. glucose		*P.J.* 300 gm. glucose	
	Control	Testosterone	Control	Testosterone	Control	Testosterone	Control	Testosterone
Actual body wt., kg.	71.0	72.4	63.4	65.0	66.9	70.7	64.3	61.3
Body wt. loss, gm.	10.7	11.2	8.6	8.2	7.6	5.3	4.4	4.0
Urinary Losses:								
Total N, mg.	190	142	136	108	106	80	96	72
Urea N, mg.	154	103	109	85	80	58	76	49
NH_3 N, mg.	15.6	17.1	9.1	9.3	4.8	3.3	5.3	5.6
Amino acid N, mg.	0.97	1.08	0.88	0.90	0.99	1.04	1.17	1.11
Creatinine N, mg.	7.3	8.5	8.1	8.0	9.1	9.5	7.7	8.7
Creatine N, mg.	1.38	0.67	1.15	0.99	2.05	0.8	1.12	0.06
P, mg.	15.8	15.7	10.3	9.5	8.8	7.6	7.5	6.5
K, meq.	0.584	0.568	0.353	0.229	0.468	0.348	0.408	0.280
Na, meq.	0.546	0.755*	0.245	0.224	0.990†	0.868†	0.043	0.058
Cl, meq.	0.391	0.526*	0.271	0.230	1.000†	0.887†	0.097	0.148
Organic acids, meq.	1.48	2.22	0.70	0.77	0.66	0.58	0.80	0.61
Acetone bodies, mg.	57.3	118.6	6.9	13.5	1.4	2.6	0.8	1.0
Milliosmols	10.9	10.6	6.4	5.5	7.4	5.5	4.6	3.4

* Because the weather was hot during this period, the loss of water, sodium and chloride was probably greater than it should have been.

† The subject received 4.5 gm. of NaCl during these periods.

while on and while off testosterone are plotted in figure 10. The values for the nitrogen excretion of *W.H.* during days three to six of his control experiment correspond closely to those of Benedict's subject, *L.* On the other hand, during days three to six of the

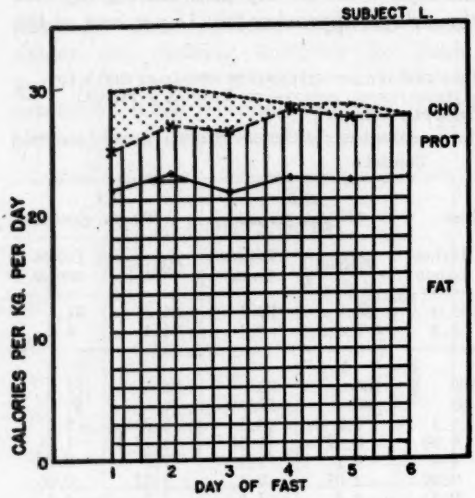

FIG. 9. A diagram of the calculated sources of energy for Benedict's subject, *L.*, during the first six days of his 30 day fast (25). The checkered area indicates the calories derived from the oxidation of fat; the vertically lined area, those derived from protein; and the speckled area, those derived from carbohydrate according to the scale given along the left hand ordinate.

experimental period on testosterone propionate, *W.H.* excreted about 0.05 grams per kilogram per day less nitrogen in the urine. In terms of total daily difference for *W.H.* this amounts to a reduction of 3.6 grams (0.05 gm. per kg. $\times$ 73 kg.) of urinary nitrogen or approximately 25 per cent. This indicates that approximately 22 grams less of body protein were catabolized per day. Such a decrease in protein catabolism would diminish the calories from that source by about 90 calories per day or five per cent of the daily energy requirement. It would also reduce by 13 grams the quantity of glucose made available by deamination of amino acids (18).

Possibly this reduction in glucose explains the tendency to lower fasting blood sugar values noted above (Figure 8). The persistence of the effect of testosterone on lowering the fasting blood sugars, even when 100 grams of glucose was eaten (*E.B.*), would appear to be due to the at least partial dependence of the concentration of glucose in the blood of such an inadequately nourished individual 12 hours after the last ingestion of limited amounts of glucose upon gluconeogenesis from protein.

In view of the marked reduction in acetonuria resulting from the ingestion of 50 gm. of glucose per day (fig. 7), the 13 gm. reduction in gluconeogenically available glucose to *W.H.* in the testosterone period might explain the increase in the excretion of acetone bodies in that period (4, 19, 20, 25, 26). The diminishing effect of testosterone on acetonuria with increased ingestion of glucose, while its depression of nitrogen output continued throughout all the experiments, also supports the idea that the increased acetonuria reflected an increased fat catabolism due to caloric deficit.

Are these observed effects of testosterone propionate on an individual receiving an

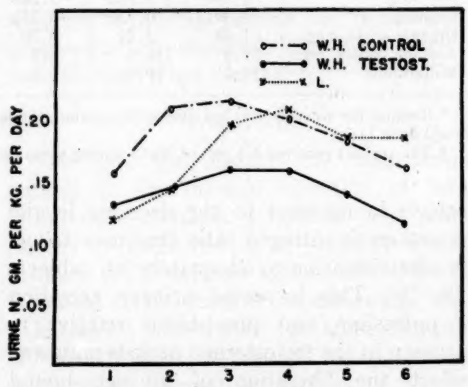

FIG. 10. The total urinary nitrogen excretion of Benedict's subject, *L.* (crosses connected by interrupted line), and of the present subject, *W.H.*, while off (circles connected by dots and dashes) and on testosterone (black circles connected by solid line) according to scale given along the left hand ordinate.

inadequate dietary intake beneficial? Viewed quantitatively the daily saving of 22 gm. of body protein for the fasting subject, *W.H.*,

amounted to about 0.2 per cent of his original muscle mass per day.[6] Such a conservation can hardly be considered important for short periods. Moreover, it was accompanied by an uneconomical expenditure of potential energy from body fat as evidenced by the ketonuria. On the other hand, the importance of such tissue protein conservation over long periods of inadequate dietary intake cannot be determined until it is known whether death from starvation results from insufficiency of fuel or from cellular depletion. Perhaps light may be thrown on this question by determining the effect of testosterone on the survival time of starving animals. Preliminary experiments with rabbits do not indicate that testosterone exerts a striking influence upon the survival period.

SUMMARY AND CONCLUSIONS

The effects of testosterone propionate therapy upon the urinary excretion of various nitrogenous substances, minerals, organic acids and acetone bodies of four healthy young men receiving an inadequate dietary intake have been studied. In addition changes in the concentrations of blood sugar and of serum electrolytes were measured.

It was found that testosterone propionate tended to reduce the urinary output of total, urea and creatine nitrogen and of potassium and phosphorus and to increase the excretion of creatinine, organic acids and acetone bodies. The effect of this agent upon body weight losses and upon the total urinary solutes (milliosmols) was appreciable but small. The administration of testosterone propionate resulted in lower fasting blood sugar values. It had little or no effect upon the concentrations of the serum electrolytes or upon the urinary elimination of amino acids or ammonia.

It is concluded that though this hormonal therapy does conserve small quantities of tissue protein under conditions of fasting, it does not result in a significant saving of body substance as a whole. There is no evidence that it diminishes the energy requirements of the starving person. Furthermore, by conserving protein, it interferes with gluconeogenesis from protein. As a consequence of the reduction in available sugar, there appears to be an increased and a less efficient oxidation of fat. With the information at hand, it is difficult to state whether or not such a conservation of protein at the expense of fat and of gluconeogenesis is beneficial for a person receiving an inadequate dietary intake.

The authors wish to acknowledge their appreciation of the eager and intelligent cooperation of the volunteer subjects which so contributed to the accuracy of these studies.

[6] The original muscle mass was estimated from the urinary excretion of preformed creatinine per day (1 gram creatinine=17.8 kg. muscle) as discussed elsewhere (27). A similar value is obtained by assuming that the musculature comprises about 45 per cent by weight of the total body tissues of a normal young man (18). The muscle mass was assumed to be 70 per cent water and 30 per cent protein (28).

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The Enhancement of Tuberculous Infection in the Guinea Pig by Steroid Hormones

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Among the many factors which long have been considered in various studies on the reaction of different individuals to infection with the tubercle bacillus, the idea of constitutional differences is even older than our knowledge of the tubercle bacillus itself. Hirsch (11) stated that phthisis (tuberculosis) appears in the successive generations of certain families too regularly to deny hereditary elements. More recent studies have established the validity of these early observations both by the experimental approach [Lurie (13)] and by the epidemiologic method [Puffer (14)]. In addition to these broader host or constitutional differences, variations in tuberculosis of similar import in the two sexes are well known.

As pointed out by Dauer (7), during the past 75 years there has been little change in the ratio of female to male mortality between 20 and 29 years of age, although total mortality from tuberculosis has been steadily declining. It appears that the factors responsible for the difference in the ratio of female to male deaths from tuberculosis has remained constant, and is unrelated to the factors to which the general decline in mortality has been attributed. Puffer (14) further pointed out that mothers (of index cases of tuberculosis in her study) born after 1860 showed the same mortality from tuberculosis as did those born prior to 1860. A sex difference is further emphasized by the observation [Dauer (7)] that tuberculosis mortality, although low, is about equal for both sexes in children less than 5 years of age, while mortality is declining much more rapidly in females over 30 years of age than in males of the same age groups. In her studies on familial susceptibility Puffer (14) also pointed out that the incidence of manifest tuberculosis in female siblings of index cases was nearly twice that among male siblings of the same families. Similarly, the incidence among female siblings of consorts was higher than that observed in the male siblings of consorts. Tuberculosis mortality, although varying with the degree of exposure, (both, one or neither parents tuberculous) was consistently higher among female siblings than among male siblings.

In addition to observations such as these on the differences in the incidence and mortality from tuberculosis between the sexes, an unfavorable effect of pregnancy in tuberculous females also has been recorded [Brack and Gray (5)], suggesting that among other factors alterations in the economy of the sex hormones in some way might result—as they appear to do in certain other diseases—in alterations in host resistance to tuberculosis. The experimental data indicate that the estrogenic substances exhibit a favorable action on a number of experimental infections. Aycock (2 a, b) showed that treatment of monkeys with estrogenic substance enhanced resistance to poliomyelitis following intranasal instillation of the virus. Sprunt, McDearman, and Raper (16) reported that treatment with estrogenic substance increased the resistance of rabbits to vaccinia virus. Von Haam and Rosenfeld (18) demon-

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strated the protective action of these substances against experimental pneumococcus infection in mice, while Foley and Aycock (8) reported similar protective action for stilbestrol against experimental streptococcal infection in mice.

Attempts to demonstrate some action—favorable or otherwise—on host resistance by the use of various endocrine hormones in experimental tuberculosis have been numerous and contradictory. Vercessi and Merenda (17), Repetti (15), Bourgeois and Bouget (3), and Gray and Brack (9) reported that various estrogenic substances exhibit little or no effect on experimental tuberculosis. Similarly, Green and Morgan (10) and Carnes and Biskind (6) reported that progesterone and testosterone respectively did not affect the course of the experimental disease. Conversely, Addessi (1) reported that rabbits treated with pregnant mare's urine died sooner of bovine tuberculosis than did normal control animals infected with the same strain. Bourgeois *et al.* (4) found that castration of guinea pigs prolonged the survival time following injection of tubercle bacilli. Injection of estrogenic substance (folliculin) and gonadotropic hormone accelerated the course of the disease in the female guinea pig while treatment with male hormones prolonged the survival time of male guinea pigs. Long and Vogt (12) observed that ovariectomized mice developed less severe tuberculosis at the height of the disease than either intact control mice or ovariectomized mice treated with theelin. The low mortality in the ovariectomized group, and the shorter survival time in the theelin-treated group suggested that in some way ovariectomy is protective and estrus harmful with respect to experimental tuberculosis.

The discrepancies in these reported results may be due in part to the use of different hormone preparations of varying potency and to the use of different strains of tubercle bacilli—some stock cultures are of relatively low virulence. Few experiments have been reported in which chemically pure crystalline hormones of standardized potency and freshly obtained strains of human tubercle bacilli were used. Aycock has noted that monkeys treated with stilbestrol often develop an unusual spontaneous tuberculosis involving the mammary and axillary lymph system. For these reasons, the following experiments were undertaken.

METHODS

In the experiments reported here, pooled and digested sputa from active cases of tuberculosis were compared in normal guinea pigs and guinea pigs injected with crystalline estrogenic substances in oil.[1] In the first experiment, an equal number of normal intact male and female guinea pigs (12 animals) 200–250 gm. in weight were given 0.05 mg. of alpha-estradiol dipropionate (Progynon-DP)[2] subcutaneously in 0.5 cc. of sterile, sesame oil. This product although less potent than the benzoate salt, has a prolonged effect following injection. Changes in the genitalia were apparent the day following administration. Forty-eight hours after injection of the alpha-estradiol dipropionate, these animals and a similar number of male and female controls were given subcutaneously in the inguinal region 0.5 cc. of a digested pool of six sputa collected the same day from active cases of tuberculosis. After pooling, the sputa were digested by the sodium hydroxide method (Wadsworth,1939) and concentrated to 1/10 the original volume in normal saline. Thereafter the estrogen-treated animals received 0.05 mg. doses of alpha-estradiol dipropionate at intervals varying from 24 to 72 hours as indicated by examination of the genitalia. The second experiment (10 animals) was identical with the first except that the estrogen-treated animals received a total of 0.5 mg. of alpha-estradiol dipropionate as 10 doses of 0.5 mg. each at 24 hour intervals prior to injection of the sputa-digest. The animals surviving

[1] A series of control animals injected with alpha-estradiol dipropionate in sesame oil in the same manner as the tests was included in these experiments. Guinea pigs killed after two, four, six, and eight weeks of such treatment showed no gross pathologic change other than some accumulation of fat in the omentum.

[2] We wish to thank Dr. W. R. Bond, Schering Corporation, for his kindness in supplying these products.

the full course of the experiments received a total of 1.65 mg. and 3.55 mg. of alpha-estradiol dipropionate respectively in the first and second experiment.

A similar experiment was done substituting testosterone propionate (Oreton)[2] for the alpha-estradiol dipropionate. The animals treated with this substance received a total of 80 mg. as 16 doses of 5.0 mg. each in 0.2 cc. of sesame oil at 24 hour intervals preceding injection of the sputa-digest. Subsequent doses were administered as indicated by the genital reaction. Animals surviving the duration of the experiment received a total of 220 mg. of testosterone dipropionate.

All animals were observed for 56 days. Animals dying early and those surviving 56 days were autopsied and examined for gross and bacteriologic (smear) evidence of tuberculosis. Certain of the normal control guinea pigs which died suddenly within a few days of the time of injection of the sputa-digest did not show evidence of tuberculosis at autopsy (hence omitted from the tables), but did present postmortem changes suggestive of acute upper respiratory infection. Such deaths were more common in the experiments done during the winter months, and, as it happened, did not appear to occur among the estrogen-treated animals, but whether or not this represents a protective effect of the estrogen against acute upper respiratory infection is not known. Four control guinea pigs were kept beyond 56 days until they died, two at 72 days and two at 84 days respectively. The guinea pigs killed after 56 days (tests and controls) are not included in the computations. The average incubation periods represent minimal values since the experiments were terminated at 56 days. Moreover, as will be discussed later, there is some evidence that death in a tuberculous guinea pig may be a chance phenomenon, the time of death being more or less unrelated to the extensiveness of infection.

RESULTS

Since the results of separate experiments with alpha-estradiol dipropionate were essentially the same, all experiments are combined in table 1. It will be seen (table 1) that guinea pigs treated with alpha-estradiol dipropionate succumbed to injection of the sputa-digest earlier than did the normal control animals injected with the same material. Testosterone propionate appears to exhibit a similar but less marked effect, since these animals received a relatively larger dose of this substance. Tuberculosis mortality by weeks following injection of the sputa-digest is shown in figure 1. Mortality in the alpha-estradiol dipropionate or testosterone propionate-treated guinea pigs was consistently higher than that observed in the control animals.

At the end of 56 days, the period for which a guinea pig is usually kept in tuberculosis diagnostic work, the mortality in the alpha-estradiol dipropionate-treated group (91%) was significantly higher than that (47%) of the control (untreated) group (table 1). Mortality in the testosterone propionate-treated group (83%) was significantly higher than that of the control group, but did not differ from the mortality in the alpha-estradiol dipropionate-treated group. The average incubation period, as measured from the time of injection to the time of death in the normal control guinea pigs, was 50 days, 1.9 times that of the alpha-estradiol dipropionate-treated group, 26 days. The average incubation period in guinea pigs treated with testosterone propionate (34 days) was intermediate between the other two groups.

Although the control guinea pigs which survived 56 days following injection of the sputa-digest all showed evidence of tuberculosis at autopsy, the alpha-estradiol dipropionate-treated animals would have provided much earlier diagnoses (in most cases) had these been diagnostic animals. In addition to the shorter average incubation period and the higher mortality, it was observed that the alpha-estradiol dipropionate-treated animals presented evidence of a much more severe, generalized tuberculous infection than did the normal controls. The distribution and frequency of tuberculous lesions in the testosterone propionate-treated group resembled that of the alpha-

estradiol dipropionate-treated group but in general, infection was less severe. The frequency with which tuberculous lesions were observed in different organs in the three groups of animals is summarized in table 2.

In view of these results, the effect of estrogenic substance on the course of experimental tuberculosis in castrate animals was studied in a smaller series of guinea pigs. Bilateral ovariectomy was performed on 10 normal female guinea pigs of 200–250 gm. in weight. Seven weeks later these animals were divided into two groups, one of which was treated with 0.6 mg. crystalline diethylstilbestrol[3] administered as 0.1 mg. doses in 0.5 cc. sterile peanut oil subcutaneously at 24 hour intervals. These and the control animals were then given 0.5 cc. of a sputa-digest collected and treated as previously described. At the same time, an identical experiment with diethylstilbestrol was done with a similar number of intact female guinea pigs. The test-animals were given 0.1 mg. doses of diethylstilbestrol at regular 24 hour intervals (except week-ends).

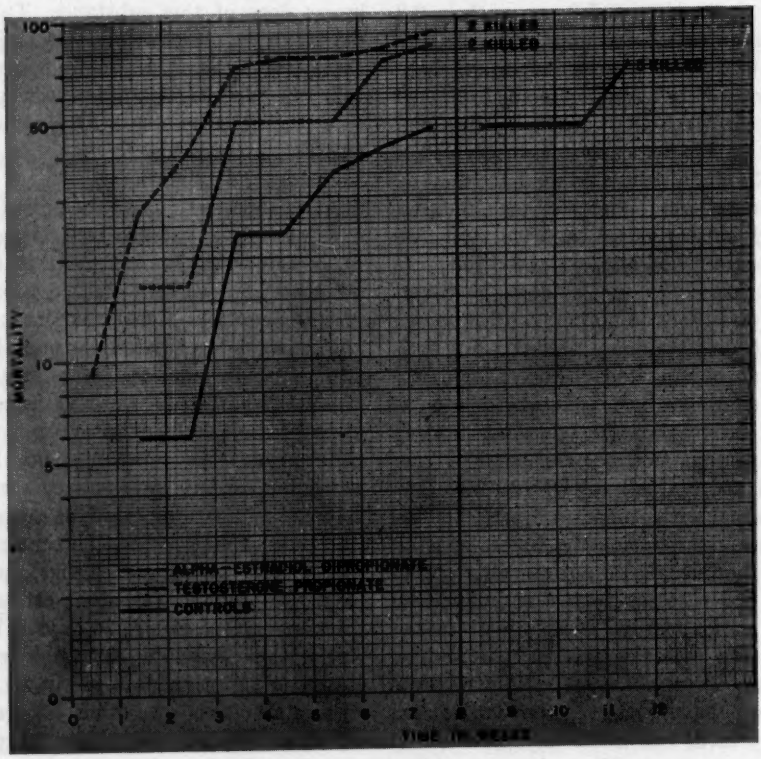

FIG. 1. Cumulative Mortality in Hormone-treated and Control Guinea Pigs Injected with Pooled Sputa-digest from Active Cases of Tuberculosis

Animals surviving the entire course of the experiment received a total of 3.3 mg. diethylstilbestrol. All survivors (56 days) were killed and autopsied. Although the series is small, the results (tables 3 and 4) with diethylstilbestrol in castrate and intact female guinea pigs were consistent with those of the previous experiments. The severity of the disease, as judged by the distribution of tuberculous lesions at autopsy was similar to that observed in the other experiments, *viz.*, the diethylstilbestrol treated animals,

[3] Product of E. R. Squibb & Sons.

TABLE 1. EXPERIMENTAL TUBERCULOSIS IN HORMONE-TREATED AND NORMAL GUINEA PIGS: AVERAGE INCUBATION AND MORTALITY

Hormone	No. animals	No. deaths in 56 days	Mortality 21 days	Mortality 56 days	Average incubation	Survived 56 days
Alpha-estradiol dipropionate	22	20	40.9	90.8	26.4 days	2*
Testosterone propionate	12	10	16.6	83.1	34.0 days	2†
None—normal controls	17	8	5.9	47.0	49.9 days	9‡

* At autopsy 1 pig had tuberculosis, 1 was negative.
† At autopsy both pigs had tuberculosis.
‡ At autopsy all pigs had tuberculosis.

TABLE 2. EXPERIMENTAL TUBERCULOSIS IN HORMONE-TREATED AND NORMAL GUINEA PIGS: ANATOMICAL DISTRIBUTION OF LESIONS AT AUTOPSY

Site of lesion	Treated animals: Alpha-estradiol dipropionate		Treated animals: Testosterone propionate		Untreated controls	
	Dead in 56 days (20 pigs)	Survived 56 days (2 pigs)	Dead in 56 days (10 pigs)	Survived 56 days (2 pigs)	Dead in 56 days (8 pigs)	Survived 56 days (9 pigs)
Inguinal nodes	20	1	10	2	8	9
Mesenteric nodes	14		4			2
Other lymph nodes	11	1	6			2
Liver	17	1	6		6	9
Spleen	20	1	10	2	8	9
Lungs	16		3			
Kidney	1					
Diaphragm	10		4			
Intercostal spaces	8		2			
Intestine	2		—	—		
None	—	1	—			

TABLE 3. EXPERIMENTAL TUBERCULOSIS IN DIETHYLSTILBESTROL-TREATED AND CONTROL GUINEA PIGS: AVERAGE INCUBATION AND MORTALITY

Treatment	No. animals*	No. deaths in 56 days	Mortality	Average incubation	Survived 56 days†
Diethylstilbestrol	5 castrate	3	60.0	31 days	2
	5 intact	4	80.0	29 days	1
None—controls	5 castrate	1	20.0	54 days	4
	6 intact	3	50.0	41 days	3

* All females.
† All survivors had tuberculosis at autopsy.

both castrate and intact, showed evidence of a severe, generalized infection similar to that observed in animals in the previous experiments with alpha-estradiol dipropionate.

DISCUSSION

Titration experiments usually consider fatality as an endpoint. A given dose of virus seldom kills all animals injected with it, nor will a given dose of a biological or drug invariably protect all animals against a given dose of virus. On the other hand, an experimental animal injected with a given dose of virus may have received multiples or fractions of the M.L.D. Similar variations are encountered with substances which protect against (or enhance) infection.

The effect of treatment with biologicals or drugs may be reflected in: 1) incubation period, 2) clinical severity, 3) survival, and

TABLE 4. EXPERIMENTAL TUBERCULOSIS IN DIETHYLSTILBESTROL-TREATED AND CONTROL GUINEA PIGS: ANATOMICAL DISTRIBUTION OF LESIONS AT AUTOPSY

Site of lesion	Treated with diethylstilbestrol				Untreated controls			
	Dead in 56 days		Survived 56 days		Dead in 56 days		Survived 56 days	
	Castrate (3 pigs)	Normal (4 pigs)	Castrate (2 pigs)	Normal (1 pig)	Castrate (1 pig)	Normal (3 pigs)	Castrate (4 pigs)	Normal (3 pigs)
Inguinal	3	4	2	1	1	3	4	3
Mesentery	3	4	2			1*		
Other lymph	3	3	2	1		1*		
Liver	3	4	2	1	1	3	4	3
Spleen	3	4	2	1	1	3	4	3
Lungs	3	4	2	1		1*	1	
Kidney	1		1					
Diaphragm and intercostal spaces	3	4	2					
Other	1							

All female guinea pigs.
* This animal resembled the diethylstilbestrol-treated animals at autopsy.

4) mortality. Incubation periods and clinical severity (clinical severity not usually practical in experimental disease) are considered and measured in terms of survival but such measurements do not go beyond the death of the animal. In general, it is difficult to go beyond this endpoint, but in experimental tuberculosis one can in a sense express mortality in terms of "degree of mortality" as judged by the extensiveness of the lesions. From tables 2 and 4 it is evident that differences between the treated and un-

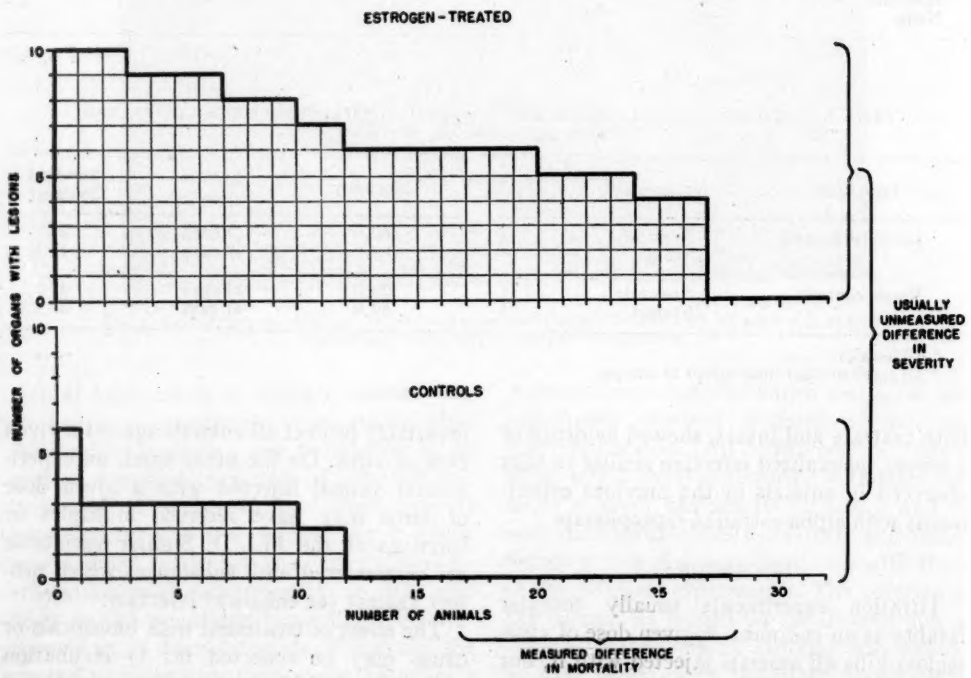

FIG. 2. Comparative Severity of Tuberculosis (number of organs involved) in Estrogen-treated and Control Guinea Pigs

treated guinea pigs, when fatality is taken as an endpoint, may not necessarily reflect the total differences among the different groups. Aside from the usual measured differences between survival and death, there are not only differences in the "degree of survival" as judged by a comparison of the incubation periods and total survivors, but differences in "degree of mortality" as well. If the extent to which the infection is generalized may be taken as a measure of the "degree of mortality," then an estimate of the total effect of treatment should include the "degree of mortality" as measured by the extent of the lesions in the dead animals. In figure 2, both the survival and mortality of all estrogen treated and control guinea pigs, and the extent of the tuberculous lesions in the dead animals are plotted schematically so as to illustrate the differences in the extent of tuberculous infection as judged by the anatomical distribution and frequency of lesions observed at autopsy. Tuberculous lesions were observed in a maximum of 10 organs for the present purpose. This method is conservative since it is based on presence or absence without considering the extent of a tuberculous lesion in a given organ. The quantitative differences in mortality between the estrogen-treated animals and the normal control guinea pigs to infection with the tubercle bacillus is reflected on the vertical axis in figure 2. Such differences usually cannot be read in experimental disease—the usual readable differences being those which appear on the horizontal axis—survival and death, with death as the endpoint.

Attempts to correlate the distribution of lesions with length of survival time indicated that the time of death is not a good measure of the extent of tuberculous lesions. It is not entirely clear why control guinea pigs dying should have on the average much less extensive lesions than estrogen-treated animals dying at the same time. In both the treated and untreated groups guinea pigs dying early in the course of the experiments showed the same "degree of severity" as those surviving for longer periods. However, regardless of survival time (incubation), the difference in the "degree of severity" between the estrogen-treated and untreated animals was consistent. The imperfect correlation between extent of tuberculous lesions and survival time suggests that in the guinea pig some factor of localization and extent within an organ may be more closely related to the moment of death than the severity of infection as judged by the number of organs involved.

SUMMARY

Guinea pigs under treatment with alpha-estradiol dipropionate, testosterone propionate, and diethylstilbestrol in oil, and normal guinia pigs of the same age and sex, were inoculated with sputum from patients with active tuberculosis. The group treated with diethylstilbestrol included both intact and castrated females.

These hormonal preparations induce a decrease of resistance of the animals to experimental tuberculosis. This was shown by three measurable differences in the results of inoculation; *i.e.*, the average intervals between inoculation and death; the total mortality at different times; and the severity of infection as judged by the extent of lesions in the animals.

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Some Observations on the Use of Thiobarbital as an Antithyroid Agent in the Treatment of Graves' Disease[1]

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Thiouracil is now extensively employed in the treatment of hyperthyroidism and it is clear that the one drawback to its use is the occasional incidence of serious toxic reactions. Currently it would appear that one out of each hundred treated cases has developed agranulocytosis and as a consequence one in each thousand has died. While this constitutes a low mortality rate for a serious disease especially when compared with the death rate associated with surgical therapy, it would be most desirable further to reduce or to eliminate it. The more common side reaction from thiouracil, drug fever, while not a serious complication in itself usually requires that the drug be discontinued and the disease treated in some other way. As there are, as yet, no specific or certain methods of preventing or treating such drug reactions, the investigation of antithyroid compounds has continued with the aim of finding a substance superior to thiouracil for clinical use. To this end, thiobarbital has been tested in man, and while the results show that the aim has not been achieved the data obtained seem worthy of record.

Thiobarbital (5,5-diethyl-2-thiobarbituric acid) differs from barbital only to the extent that one oxygen atom is replaced by an atom of sulfur. It is only moderately active as a sedative or hypnotic (7), and in common with many other thiobarbiturates large doses in animals exhibit both a depressant and a stimulating effect upon the nervous system. When surgical anaesthesia is induced the animals retain hyperactive reflexes and appropriate stimuli give rise to convulsive movements. Its property of inhibiting the endocrine function of the thyroid gland seems to be dependent upon the presence of the sulfur atom at position two and upon the two substituents on carbon atom number five. A number of other thiobarbiturates which meet these requirements, including the widely-used intravenous anaesthetic, pentothal, also have antithyroid activity (1), but on the basis of tests in rats thiobarbital is the most active of more than 30 thiobarbituric acid derivatives that have been assayed (4). Its antithyroid activity is manifested by doses which are well below those required to produce sedation. When administered to rats in small doses thiobarbital appears to be somewhat more active than thiouracil and slightly less toxic as judged by the rate of growth. Large doses seem to be less effective but much more toxic than comparable doses of thiouracil (1, 3). The prolonged administration of this and other thiobarbiturates in dogs and in rats has been found to result in no anatomical changes except a fatty infiltration of the liver (12, 3).

CLINICAL DATA

Observations on the effect of this compound[2] in man have extended over 16 months

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[1] Aided in part by grants from the Committee on Endocrinology of the National Research Council and from the American Cyanamid Company.

[2] Thiobarbital was generously supplied by the Abbott Laboratories, North Chicago, Illinois and the Lederle Laboratories, Inc., Pearl River, New York.

TABLE 1

Case No.	Age and sex	Initial wt.	Other diagnoses	Dosage Grams/day*	B.M.R. Initial	B.M.R. Subsequent†	Complications and toxic effects	Comments
Hyperthyroidism								
1	52M	126	Thiouracil sensitivity	0.2(40) 0.15(50)	+45	− 1(16)	Died, liver disease—see text	
2	72F	107	Diabetes Pyelonephritis	0.2(29)	+30	+16(28)	Drug fever 4th to 11th day. Died, agranulocytosis—see text	
3	23F	101		1.0(1) 0.2(96) 0.1(69)	+54	+ 8(29)	Early myxedema 4th month	Complete remission‡ 6 months
4	60F	96		1.0(1) 0.2(7) 0(4) 0.2(83) 0(11) 0.2(3)	+33	+ 8(21)	Drug fever 7th to 11th day. Again after intermission	Changed to another compound
5	46F	126	Angina pectoris	1.0(1) 0.3(84) 0.2(56) 0.1(56)	+37	+ 6(28)	None	Complete remission 5 months. No cardiac symptoms
6	32F	118	Pregnancy	0.5(1) 0.3(60)	+21	+ 2(41)	None	Initial response good—subsequent course unknown
7	23F	125		1.0(1) 0.3(85) 0.2(28) 0.1(56)	+34	+18(14)	Early myxedema 4th month	Complete remission 2 months
8	50F	91		0.5(1) 0.3(4) 0.2(5) 0(3) 0.2(146) 0.1(93) 0.05(30+)	+77	+33(9)	Drug fever 8th to 12th day. Early myxedema 6th month	
9	28F	110		0.2(125)	+43	+15(68)	Drug fever second week	Changed to another compound at 4 months
10	55F	103	Congestive heart failure	0.2(13) 0.1(75)	+24		Malaise, headache second week	Complete remission 8 months
11	42F	127		0.2(38)	+10	− 9(76)	None	Discontinued because diagnosis uncertain
12	61F	122		0.2(32)	+43	+21(32)	None	Changed to another compound
13	45F	107	Thiouracil sensitivity	0.1(40) 0(16) 0.05(19)			Fever and leukopenia both occasions	
14	51F	118		0.1(106) 0.05(28) 0.025(28)	+21	− 6(44)	None	Complete remission 3 months
15	54M	160		0.1(72+)			Lobar pneumonia	
16	56F	124		0.1(153+)			None	Good clinical response
17	50M	114		0.1(51+)			None	
18	46M	148		0.1(195+)			None	Good clinical response
			Pretreated with Iodine					
Hyperthyroidism								
19	47M	123	Auricular fibrillation	0.2(186) 0.1(69) 0(49) 0.1(60+)	+35	+ 6(90)	Early myxedema 6th month	Fibrillation reverted with quinidine
20	53M	142	Cholecystitis Arthritis	0.5(1) 0.2(95)	+30	+ 7(80)	None	Inadvertently discontinued—complete remission 8 months
21	58M	121		0.2(28) 0.3(76) 0.2(7) 0.1(28) 0.05(126)	+71	+16(50)	None	Complete remission 2 months
22	74F	120	Congestive heart failure	0.2(182)	+43	+28(70)	None	Complete remission 4 months
23	46F	147	Partial ophthalmoplegia	0.1(40+)	+47		None	Cardiac failure not improved
No Thyroid Diseases								
24	73F	112	Hypertension Angina	0.2(7) 0(11) 0.2(22)			Drug fever both occasions	Not improved
25	54F	91	Rheumatic heart disease; failure	0.4(8) 0.2(105)			Somnolence on larger dose	Not improved
26	59F	134	Myasthenia	0.1(14)			None	Discontinued because diagnosis uncertain
27	46F	103	Hypertensive heart disease	0.2(8)			Lassitude and headache	
28	52F	106	Conjestive heart failure	0.5(1) 0.3(8) 0(4) 0.1(4) 0.2(52)			Drug fever 8th to 13th day	Not improved
29	50F	141	Congestive heart failure	0.4(10) 0.2(245)			Somnolence on larger dose	Goiter and myxedema 6 months. Not improved
30	32F	108	Addison's disease	0.3(1) 0.2(5)			None	Discontinued because diagnosis uncertain

* The figures in parentheses after each dosage are the number of days that the dose was given. The + sign indicates that treatment is still being given.

† The subsequent B.M.R. value is one reading selected to give an index of the rate of response. The figures in parentheses indicate the number of days of treatment before that reading was taken.

‡ By complete remission is meant a continued absence of subjective and objective evidence of hyperthyroidism after therapy was discontinued.

since February, 1944. In all, 30 cases are included in this report, 23 of these being clear instances of hyperthyroidism. The remaining seven patients included four who suffered from advanced cardiac decompensation and three in whom the diagnosis of hyperthyroidism was in doubt. The patients with no evidence of thyroid disease are included for the purpose of better evaluating the incidence of the side effects of the drug.

Five additional patients received thiobarbital for a few days only, and as no metabolic or toxic effects were observed these have been omitted from this report.

The pertinent data illustrating the effectiveness of this compound and its toxic effects are given in table 1. The first 18 patients listed gave no history of recent iodine therapy. The next five had received full doses of iodine up to the time thiobarbital

was begun. The last seven patients are considered to have had no disturbance of thyroid function.

The dosage and duration of treatment is shown in full. With the exception of seven patients who are still under treatment the total duration of therapy is recorded. In almost all cases the medication was given at twelve hour intervals, a few received three doses daily and several were given their total daily dose once each day.

The initial metabolic rate shown in the table usually represented the minimal level reached before therapy was begun but some of the values are averages of the pretreatment determinations. The one subsequent value shown was selected to show the rate of the metabolic response. All complications and intercurrent events which might possibly have been attributed to the medication are listed in the table. Some of these may not have been side effects of the drug as noted below.

The initial metabolic response in a series of nine selected cases is shown in figure 1 which includes eight patients who had not recently received iodine and who were followed by sufficiently frequent metabolic rate determinations to insure a satisfactory record of the response. It is clear that the metabolic responses are quite as prompt as a similar group of ten patients of comparable severity treated with thiouracil.

Clinical improvement followed the declining metabolic rate and no consistent difference could be detected between this compound and thiouracil as to the rate and degree of symptomatic improvement.

The eventual result of continued treatment was quite as satisfactory as that noted with thiouracil. In eight cases a sustained remission followed when the treatment was discontinued. In one patient (*No. 19*) a recurrence of the manifestations of hyperthyroidism followed when the drug was withdrawn after eight months of continuous treatment. This man had previously undergone a two stage subtotal thryoidectomy and evidence of hyperthyroidism and auricular fibrillation had been present since his discharge from the army in 1918; the gland was large and nodular. Thiobarbital was discontinued and substituted by another compound in three instances; only in case 4 was this done because of intolerance to the drug.

Dosage

The dosage used in the first 22 patients was most often 0.1 gm. at 8 or 12 hour intervals (0.2 to 0.3 gm. per day), and it was not realized that this dosage was unnecessarily large until an opportunity was provided of observing the results of prolonged treatment. Indeed in seven patients therapy was initiated by the administration of a single dose of 0.5 gm. or a total dose of 1.0 gm. during the first 24 hours. This was done with the aim of achieving an effective concentration in the body promptly. It was later apparent that this only served to increase the already excessive dosage. It may have been a rational procedure had the subsequent dosage been considerably reduced. However three of the six instances of drug fever occurred among the seven patients who received a large priming dose, suggesting that this procedure favors the occurrence of side effects.

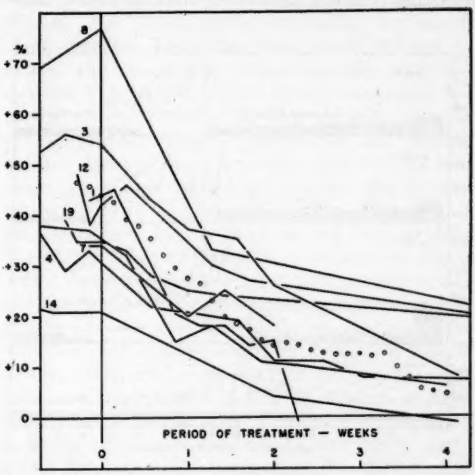

FIG. 1. Rate of decline of the metabolic rate of nine patients with Graves' disease. None except *number 19* had recently received iodine. The open circles represent the average rate of response of ten comparable patients treated with thiouracil as previously reported (2).

When treatment had been continued for several months, evidence of hypothyroidism was observed in a number of patients. It was not until then that the greater effectiveness of this compound was fully realized. Eventually five patients in all were observed to develop definite manifestations of myxedema; this was accompanied by thryoid enlargement, a phenomenon consistently associated with excessive maintenance dosage. The doses which proved to be excessive for maintenance were 0.1 gm. twice daily in four and 0.1 gm. once daily in one. In two of the former cases a dosage of 50 mg. twice daily was also found to be excessive, while at the other extreme in only one case (*No. 19*) was a dose of 0.1 gm. once daily found to be inadequate; when 50 mg. twice daily was substituted in this instance, adequate maintenance was achieved.

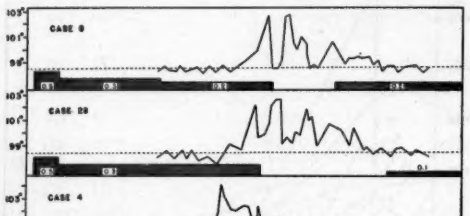

FIG. 2. Temperature charts of four patients who exhibited a febrile response when treated with thiobarbital The base line in each case is at 98.6°F. The temperatures during the period of elevation were taken rectally except in *case 2*. The dosages of thiobarbital are shown by the shaded areas.

The last eight cases to be treated received only 0.1 gm. daily; in three of them the dose was given once daily, in the others it was divided and given at 12 hour intervals. Each of these cases has responded in a satisfactory manner. It may be significant that only one toxic reaction (*case 13*) was observed among these eight cases and this was not proved to be caused by the drug.

TOXIC EFFECTS

As far as can be determined from the medical literature thiobarbital has never before been administered to man. For this reason all untoward events occurring during the course of therapy in each case have been recorded, and it will be assumed that the drug was directly or indirectly responsible until such time as a wider experience with this compound should show otherwise.

Sedative effect

When one half or one gram was given as a single dose or in divided doses over the course of the first day noticeable drowsiness or somnolence followed in five of seven cases usually on the day after. The two cases given 0.4 gm. daily became most uncomfortably somnolent after five to seven days of therapy. Two out of six cases receiving 0.3 gm. daily complained of lassitude and drowsiness after a week had passed. The daily administration of 0.2 gm. was not followed by a noticeable sedative effect in any of 20 cases. Clearly these side effects were due to the drug and were to be anticipated from its known hypnotic properties, indeed in some instances the larger doses were given deliberately in order to estimate the dosage which would have a sedative effect in man. It is perhaps significant that the patients usually complained of the drowsiness as if the sensation was an unpleasant one.

Drug fever

A definite febrile response, in all probability related to the administration of thiobarbital, occurred in six patients. The fever began on the fifth to eighth day of treatment, increased slowly in intensity until a body temperature of 102° to 105° F. was reached and then declined; (fig. 2) the febrile periods lasted for as long as seven days even though the drug were immediately withdrawn. Profound malaise accompanied the fever and usually there were pains in the muscles especially those of the neck, shoulders and back. No skin eruptions, lymph gland enlargement or edema were observed. The leukocyte count remained normal or was slightly elevated

and the granulocyte percentage was within the upper region of normal. When the fever had subsided the drug was readministered without evoking a second febrile response. This course of events was so different from that observed in drug fever from thiouracil that three cases were observed before it was clear that the drug was responsible for the fever. Indeed two cases continued to receive the drug throughout the course of the fever and in these the duration of the fever was not appreciably prolonged. In four cases thiobarbital was continued for periods of two, three, four and ten months respectively after the febrile episode without further manifestations of toxicity or sensitivity. In *case 4*, however, readministration of thiobarbital after a brief intermission at the end of three months' therapy evoked a second febrile response, and case 24 continued to run a slight fever when the drug was continued after the acute febrile episode had passed.

A seventh patient (*case 13*) experienced three mild febrile illnesses, one while receiving thiouracil and two while taking thiobarbital. Each was accompanied by leukopenia and no organic disease or localizing signs of infection could be found. There was no constant relationship between the time of onset of these disorders and the duration of treatment and the medications cannot with certainty be incriminated. Two patients (*cases 10* and *27*) experienced malaise, lassitude and headache without fever during the second week. It is possible that these patients experienced a reaction similar in kind to drug fever, but of such mild degree as not to disturb temperature regulation. They are of especial interest in possibly pointing to an explanation of the febrile response. As noted above, the larger daily doses often gave rise to somnolence and lassitude after a week of treatment indicating a cumulative effect maximal at that time. Perhaps the mild constitutional reactions and the fevers which occurred during the second week of treatment are also indications of an excessive accumulation of thiobarbital or of one of its degradation products in the body.

Two patients in this series died while taking thiobarbital, one of rapidly progressive liver disease and one of agranulocytosis. The details of these two cases were as follows:

Case 1. A man of 52, having a typical case of Graves' disease of six months' duration with minimal ocular signs and slight thyroid enlargement, was treated with thiouracil beginning on June 1, 1943. Response of treatment was prompt and the disease was satisfactorily controlled for about three months. Thereafter the patient refused to attend the out-patient clinic regularly and discontinued the medication on several occasions; hyperthyroidism returned. During the nine months of intermittent thiouracil treatment the patient suffered from pharyngitis, was subjected to tonsillectomy in another hospital, and experienced several episodes of ill health the nature of which was not determined. Finally he concluded that the drug caused him to be unwell, and he refused to take it any longer. In view of the severity of the hyperthyroidism and the previous difficulties in managing this patient at home he was admitted to the hospital for treatment with thiobarbital which was given in a dose of 50 mg. every six hours (0.2 gm. daily). The basal metabolic rate fell from +45% to −1% in 16 days and remained normal after the dosage was reduced to 50 mg. three times daily on the 30th day of treatment. The body weight increased from 126 pounds to 153 pounds in two months and the patient had resumed work as a day laborer. Just three months after thiobarbital was started, there developed malaise, weakness, loss of appetite and marked fatigue. Two days later the urine was noted to be dark and the stools light in color, and after two more days the skin became noticeably yellow and he entered the hospital for the third time. Medication was discontinued on the day before admission.

There was deep jaundice; the liver to palpation appeared to be greatly enlarged though it was of normal size on x-ray examination. The urine contained bile and urobilinogen; the feces were light brown. Detailed clinical and laboratory examinations failed to establish a definite diagnosis. The jaundice deepened and the patient died in coma on the eighth hospital day. A post mortem examination was not permitted.

Case 2. A woman of 72 years was admitted to the hospital in diabetic coma. She was not previously known to have suffered from diabetes but after recovery from coma there persisted a severe diabetes which was difficult to regulate with large doses of insulin. Because of persistent pyuria and low grade fever a diagnosis of pyelonephritis was made and sulfadiazine was administered in full dosage for nine days. During convalescence a number of features suggested the coexistence of thyrotoxicosis; the pa-

tient was alert and active, the skin was warm and moist and the eyes were bright and the palpebral fissures wide. The pulse rate was usually over 100 beats per minute at rest and the basal metabolic rate was found to be +30 and +35 on three tests.

Thiobarbital was given in a dose of 0.1 gm. every twelve hours. During the sixth to tenth days of treatment there was a return of fever (see fig.2) which subsided even though the drug was not withdrawn; this was interpreted as drug fever though the possibility that it was a further manifestation of pyelonephritis could not be excluded. During the fourth week of treatment the patient complained of weakness and lassitude and the temperature was elevated in the evenings to 99° to 100.5°F. On the 29th day the total leukocyte count which previously had varied between 5,700 and 9,400 was found to be 750 and no granulcytes could be found in the smear. Thiobarbital was discontinued and treatment with penicillin, increased dosage of vitamins, crude and purified liver extract and pentnucleotide was instituted at once. For four days the patient showed no localizing evidence of infection and the temperature reached maximal levels of 101° to 102.8F. Because of a mild anemia which had been noted since admission a transfusion was given on the fifth day of the disease; this was promptly followed by a chill and the temperature rose to 105.6°F. During the next two days the high fever continued and the patient died eight days after the diagnosis of agranulocytosis was made. On the day of death *E. coli* was grown from the blood and at post mortem examination an abscess was found in the sternum at the site of three aspiration biopsies of the sternal marrow. Other medications given during the course of thiobarbital therapy were insulin, various vitamin preparations, digitalis, aspirin, whisky and phenobarbital. There was no evidence that the various forms of treatment directed toward a stimulation of granulopoiesis were of any benefit. The total leukocyte count varied between 600 and 1600, and no granulocytes appeared during the eight days.

DISCUSSION

These studies serve to show that thiobarbital is more active gram for gram than thiouracil in inhibiting thyroid function in man. Given at eight or twelve hour intervals the minimal initial dosage of thiouracil which will control the majority if not all cases of hyperthyroidism has proven to be 0.4 gm. daily though 0.2 gm. has been sufficient in some cases. In the present study 0.2 gm. of thiobarbital has not failed to be effective and 0.1 gm. was adequate in all eight instances. Thus it would seem that thiobarbital is a little more than twice as effective as thiouracil. The average maintenance dose of thiouracil is 0.2 gm. daily in two doses at 12 hour intervals while these studies indicate that the maintenance dose of thiobarbital averages 0.1 gm. daily or somewhat less. This again would indicate that thiobarbital is more than twice as active as thiouracil.

The data also show that a single oral dose of thiobarbital has a more prolonged action than a single dose of thiouracil. It is now well recognized that the effectiveness of thiouracil is greatly diminished if the doses are spaced at 24 hour intervals instead of at eight or twelve hours (2). Thiobarbital on the other hand has been quite effective even when only one dose is given per day. In several instances, however, there was an opportunity to observe that a dose of 50 mg. every twelve hours was distinctly more effective than a single daily dose of 100 mg.

Although a fairly good approximation of the minimal effective dose of thiobarbital can be obtained from this small series of cases, the data are entirely inadequate to permit an analysis of its toxic effects. In this series there was a very high incidence of side effects, but there is some uncertainty as to whether all of them were caused by the drug. Some of them, however, were probably toxic effects and the result of excessive dosage. As this compound seems to be degraded or eliminated at a slow rate, at least at a rate slower than that of thiouracil, its effects would tend to be cumulative. This possibility receives support from the observation that several patients began to be drowsy only several days or a week after starting to take the compound in a dose of 0.3 or 0.4 gm. daily. Perhaps the high incidence of drug fever was in part due to this cumulative quality and if so it would seem reasonable to expect that it would be less likely to occur if the minimal effective dosage were not exceeded. Furthermore the febrile response appears to be entirely benign and the drug can usually be continued; in the case of thiouracil a febrile response usually precludes further therapy with that compound.

It is not known whether the fatal liver disorder in *case 1* was caused by the thiobarbital or not. The animal experiments

(12) showing that accumulation of fat in the liver follows the prolonged administration of thiobarbiturates suggests that thiobarbital might cause liver damage in man. However none of the other treated patients showed any evidence of impaired liver function and it is well known that infectious hepatitis can give rise to a syndrome clinically indistinguishable from that observed in this patient.

The agranulocytic reaction (*case 2*) can with more assurance be attributed to the thiobarbital therapy. The analogy with thiouracil is most suggestive; the agranulocytosis was detected on the 29th day of treatment and the case was complicated by infection and diabetes, features which have commonly been associated with the agranulocytoses caused by thiouracil.

In spite of this most unfavorable record this compound would appear to be of value in the treatment of hyperthyroidism and to deserve further study. Used in the proper dosage and with due consideration of the toxic effects to be anticipated, more favorable results should be obtained. Also a small series of cases such as this can give a very untrue picture of the real nature of a substance. For example, the experience with thiouracil in the series published from different clinics has been most divergent as to the incidence of toxic effects. Some reports show an unnusually high incidence of serious complications; for example, Lozinski and Siminovitch (8) recorded one death from agranulocytosis among five treated cases and Evans and Flink (6) encountered five serious toxic reactions among 26 cases. On the other hand no serious toxic reactions were seen in series of 100 cases reported by Palmer (11), 43 by Montague and Wilson (9), 34 by Newman (10) and more than 40 by Eaton (5).

It would appear that an appropriate dose of thiobarbital would be 50 mg. every twelve hours for the initial period of therapy in cases of the usual severity. It is possible that a somewhat smaller dose could be used in mild cases which would not be endangered should the dose prove to be inadequate. On the basis of the findings to date it would appear to be unwise to give thiobarbital in dosages of 0.2 gm. daily or higher. While a single dose in 24 hours has been effective in some instances it would seem reasonable to take advantage of the apparently greater effectiveness of the compound when it is given every twelve hours.

SUMMARY

The effectiveness of thiobarbital in the treatment of hyperthyroidism and its toxic effects have been studied in 30 cases given total daily doses of from 0.1 to 0.4 gm. All of the manifestations of hyperthyroidism were satisfactorily controlled, but in the dosage used there was a high incidence of complications. Two deaths occurred, one from agranulocytosis and one from an acute liver disorder; six cases experienced a febrile reaction during the second week of treatment, but this did not preclude continued treatment. It is estimated that thiobarbital is more than twice as active as thiouracil in inhibiting the function of the thyroid gland in man, and that it is more toxic than thiouracil when the minimal effective dose is exceeded.

ACKNOWLEDGEMENT

This study was made possible by the generous cooperation and help of the members of the resident and visiting staffs of the Peter Bent Brigham Hospital. We are especially indebted to Dr. A. W. Cantratto for permission to include five of his private patients (*cases 15*, *16*, *17*, *18*, and *23*) to Dr. J. F. Fay for permission to include *case 13*, and to Drs. J. F. Marchand, R. Macquigg, A. Roos, B. E. Lowenstein, and W. P. VanderLaan for their assistance in carrying out this study.

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LETTER TO THE EDITOR

THE USE OF GLUCOSE IN THE TREATMENT OF DIABETIC COMA

IN DIABETIC COMA the essential disturbance is the relative or absolute lack of insulin. It is a deficiency state in which the primary problems are the estimation of the amount of insulin required and its prompt administration in the first few hours of treatment. As the result of the hyperglycemia, polyuria and ketosis one finds secondary changes, such as extreme dehydration and loss of base, chiefly sodium; both are lost from intra- and extra-cellular spaces. These latter changes must be treated by the simultaneous administration of adequate amounts of water and salt. When a sufficient quantity of insulin has been given to provide a reserve making possible the normal utilization of carbohydrate, food including protein as well as carbohydrate is needed. Much confusion at present exists because of differences of opinion regarding the use of glucose by intravenous or subcutaneous administration during diabetic coma.

Possibly an overemphasis of the importance of an immediate restoration of glycogen stores in the liver is a factor in this confusion. Non-diabetic ketosis, as in starvation, pregnancy, etc., never leads to a condition clinically comparable with diabetic coma. The development of ketosis in diabetic coma is accompanied by progressive hyperglycemia. Presumably the excessive rise in sugar in the blood is due to the lack of insulin and the increasing glycogenolysis in the liver and muscles. At the height of diabetic coma the liver is usually considered to be almost devoid of glycogen. In starvation and hyperthyroidism the liver glycogen is also reduced without impairment of glucose oxidation. Indeed it has long been known that in diabetes, the starvation treatment of Allen, which certainly reduced liver glycogen, was accompanied by a rising respiratory quotient and an increase in carbohydrate utilization. There is no proof for the supposition that oxidation of glucose is prevented by absence of glycogen in the liver or that it is improved by increasing liver glycogen *per se*. However, in diabetic coma in the absence of sufficient insulin carbohydrate yields to fat as the chief substrate for oxidation in the liver. The production of ketone bodies in the liver therefore mounts steadily and exceeds the capacity of the tissues to oxidize or of the kidneys to excrete them. This is not due to a lack of available carbohydrate.

The table of the approximate carbohydrate content of human tissues given by Root[4] shows that when the blood sugar in diabetic coma is within the range of from 500 to 700 milligrams per 100 cc., there may be already present in the body fluids excessive glucose in an amount varying from 100 to 146 grams, because of the inability of the body to utilize it. Under these circumstances, if glucose is given intravenously to a patient in diabetic coma, the respiratory quotient does not rise above the level for fat as shown by Root and Carpenter.[5] Glucose administered without insulin to a patient in diabetic coma, having a CO_2 content of the blood below 20 volumes per cent, merely accelerates the downward course and may soon be followed by hyperglycemia, further dehydration, anuria and pancreatic exhaustion. The essential problem is to find the dose of insulin which will bring about oxidation of glucose so that the oxidation of fat and the consequent formation of ketone bodies may be reduced. The problem is difficult because with severe diabetic acidosis insulin resistance increases so that the insulin requirement may vary from 100 to 1,000 units.

The simultaneous administration of glucose with salt and water has been advised by Soskin and Levine[6] and by Butler.[2] These authors consider that the stores of glycogen in diabetic coma are negligible, and they hold that the sugar present in the blood and intercellular fluid is inadequate to replenish the stores of glycogen. The case discussed by Butler gives a clear picture of the effect of giving glucose to a

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child who was improving with adequate insulin treatment. The note describes the immediate return of glycosuria and acetonuria together with the fact that the patient became less responsive and respirations assumed a peculiar gasping quality. Repeatedly such unfavorable events have followed the administration of glucose in serious diabetic coma. Actually, Mirsky,[3] who studied the effect upon diabetes of the administration of large amounts of carbohydrate (500 grams or more in 24-hours), specifically warned against such therapy because of the danger of pancreatic exhaustion.

The danger involved in the administration of glucose depends upon the amount of glucose administered and the rate at which it is given. The continuous injection of glucose at a rate in excess of caloric needs leads to death even in normal animals. Astwood[1] gave glucose solution to a normal dog at the rate of 1.7 grams per kilogram weight per hour, and death resulted at the end of 70 hours. Those dogs received seven calories in the form of glucose each hour, yet their metabolic needs were only two calories per hour. A diabetic boy in coma has a total metabolism of about 70 calories per hour. If he is given 1,000 cc. of 10 per cent glucose solution in an hour's time he has received 400 calories or approximately six times his caloric need in that form. In one fatal case, that of a 19 year old boy, 350 grams of glucose had been given in a few hours without adequate insulin. At present one of the chief errors and causes of death in coma cases is the overfeeding of such patients with excessive amounts of glucose—amounts per hour greater than the caloric needs.

No one supposes that in coma the administration of glucose at the rate of perhaps 10 grams per hour would be harmful, provided a sufficient amount of insulin had been given to make possible its normal utilization. Clinical results cannot be disregarded in a field of such complexity. At the Deaconess Hospital[4] no glucose has been given to patients actually in diabetic coma since 1923. In 123 consecutive cases of diabetic coma where the blood CO_2 content was 20 volumes or less treated between August 1940 and May 1, 1944 only two deaths occurred, a rate of 1.6 per cent. Even those deaths could have been prevented by earlier admission to the hospital of one case and the omission of the large amounts of glucose given in the early treatment of the other. The low mortality was attributed to the more prompt use of large amounts of insulin. Thus, during the first three hours after admission to the hospital the average patient received 216 units of insulin; in this group were included certain profoundly unconscious patients, with blood sugar values from 800 to 1400 milligrams, who received as much as 500 units in the first three hours. A reduction of the total metabolic rate is achieved by rest in bed and the avoidance of overfeeding. After recovery from the acute stage, a diet while the patient is in bed providing approximately 20 calories per kilogram of body weight and 150 grams carbohydrate per twenty-four hours is begun. Later a diet adequate for normal activity should be resumed. Carbohydrate stores are thus gradually replenished.

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Abstracts of
CURRENT ENDOCRINE LITERATURE

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ADRENALS

PRATT, J. P. AND R. L. SCHAEFER.

Sex precocity, virilism, adrenal cortical tumor. *Am. J. Obst. & Gynec.*, (5): 623–633, (1945).

The authors reported three female patients with varying degrees of virilism. One, a thirty three month old child with marked signs of virilism, had an encapsulated tumor in the right adrenal which was removed. There was a marked reversal to that of a normal child postoperatively and six years later there was no sign of metastasis. The second presented signs of virilism at four months which increased until her death at the age of 25 months. The virilism appeared as a consequence of metastases of a fibrosarcoma of the cheek to the adrenal cortex. The third patient, eight years and four months of age, had only moderate enlargement of the clitoris, no change in voice and lacked increased statural growth. Adrenal tumor was suspected, but operation revealed no adrenal enlargement. —*C.D.D.*

ENDOCRINE GENERAL

CHRISTY, C. J.

Vitamin E in menopause. *Am. J. Obst. Gynec. 50* (1): 84–87 (1945).

The author presented a preliminary report of the clinical use of vitamin E in the treatment of the menopausal syndrome. Twenty-five patients were treated with 10 to 20 milligrams of vitamin E orally, daily over periods of from one to three weeks. Seven reported complete relief, 16 very marked relief and two no relief. There were no undesirable side reactions.

The relief of subjective symptoms coincident with the administration of vitamin E could not be distinguished from that obtained with the natural or synthetic estrogens. The chief advantage of the former was that it was free of any stimulative effect on the breast parenchyma or the genital system. The author stated that in some patients vitamin E seemed more effective in relieving vasomotor instability symptoms than estrogens.—*C.D.D.*

CINBERG, B. L.

Postmenopausal pruritis vulvae. *Am. J. Obst. & Gynec. 49* (5): 647–657 (1945).

The author reported the successful treatment of 14 patients with severe postmenopausal pruritis vulvae in which pretherapy and posttherapy vulval biopsies were obtained. The best method of obtaining relief was to protect the skin from further irritation by the constant application of a bland ointment for at least three months. The author advised the local use of an androgenic ointment (two milligrams of testosterone propionate to a gram of ointment) when there was severe vulval atrophy.—*C.D.D.*

DE LA BALZE, F. A.

Gynecomastia. *Rev. méd.-quir. de pat. fem. 21:* 309 (1943).

The author reviews the cases of gynecomastia in the literature to 1943, and gives 400 references. He reports additional cases, (1) that of a patient with Addison's disease in whom transitory gynecomastia appeared after the administration of adrenal cortical extract and also after the administration of desoxycorticosterone acetate; in both instances the gynecomastia subsided after treatment was discontinued, (2) that of a patient in whom gynecomastia and hyperthyroidism appeared simultaneously and (3) that of a patient in whom gynecomastia appeared during the development of bronchial carcinoma. The author presents an etiological classification of cases of gynecomastia. He emphasizes two factors in the pathogenesis of this condition (1) the predisposing or chromosomal factors (i.e., the "zygotic make-up" of the individual); this can also be called "potential local feminization" or intersexuality localized in the breast, and (2) the factor which induces the appearance of gynecomastia in the breast prepared by factor

(1); this factor is usually an alteration in the kind or the amount of steroid in the body fluids (in most cases this factor is an excess of estrogens).—*F.A. de la B.*

HAC, L. R., H. C. HESSELTINE, F. L. ADAIR and M. B. CRUDIM

Sulfonamide and stilbestrol therapy in gonococcal vulvovaginitis. *Am. J. Obst. & Gynec. 50* (1): 88–95 (1945).

Of 135 children treated with sulfanilamide, sulfapyridine or sulfathiazole, 89 percent responded satisfactorily to sulfapyridine or sulfathiazole. Sulfanilamide is definitely contraindicated because of a higher percentage of failures and because it tended to produce sulfa-resistant strains of gonococci. Diethylstilbestrol was found useful in the treatment of sulfonamide resistant patients.—*C.D.D.*

LEFF M.

The comparative action of posterior pituitary and ergonovine in the third and fourth stages of labor: Observations based on 5000 deliveries. *Am. J. Obst. & Gynec. 49* (6): 734–738 (1945).

Ergonovine was given intravenously or intramuscularly as soon as the placenta was expressed in 2500 deliveries. Despite firm contraction of the uterus, bleeding occurred and frequently persisted. Much better results have been obtained in a subsequent series of 2500 deliveries by the use of pituitary extract immediately after the placenta was delivered and the postponing of ergonovine injection for 20 minutes.

The better results with the combined therapy was believed due to the fact that posterior pituitary substances cause both contraction and retraction of the uterus and produce retraction of the cervix whereas ergonovine causes a tonic contraction of the uterus but no retraction.—*C.D.D.*

QUIGLEY, J. K.

Habitual abortion. *Am. J. Obst. & Gynec. 49* (5): 633–641 (1945).

The author reported that 28 of 30 women who had had one or more previous spontaneous abortions went to full term or near it and gave birth to normal children when treated by the usual conservative measures and intramuscular progestin, five units every four days. The author advised painstaking investigation of both husband and wife before pregnancy was attempted.—*C.D.D.*

RAICES, A. E., E. B. DEL CASTILLO AND M. GAMBIN.

The 17-ketosteroids in virilization of the adult woman. *Medicina, Buenos Aires 5;* 152 (1945).

The urinary 17-ketosteroid excretion was determined on 75 virilized women. In 26 patients the values were normal; in 49 the values were above the normal level, and in 22 of these the excretion was greater than 30 mg. per 24 hours. In one case of adrenal hyperplasia the values were low (4.8 and 3.2 mg. per 24 hr.), and in one case of adrenal tumor the values were normal (12.3, 9.3, and 6.3 mg. per 24 hr.). A high level of excretion was found in patients without any manifestations of adrenal hyperplasia or tumor. Discrepancies in the 17-ketosteroid excretion of several other patients are discussed. The authors conclude that in adult women with virilization the urinary 17-ketosteroid levels may be normal although elevated values are usually present.—*F.A. de la B.*

SHUTE, W. AND E. SHUTE

The effect of dihydrotachysterol on certain toxemias of late pregnancy. *Surg., Gynec & Obst. 81:* 83–92 (1945).

The effect of combined dihydrotachysterol and calcium therapy on a series of 42 cases of toxemia of late pregnancy was studied. Four of the patients were of the low estrogen or true preeclamptic type and 38 were of the high estrogen type. The therapy proved ineffective in the true preeclamptic group but was thought to have benefited 42 percent of the high estrogen group. The improvement was manifest chiefly in a lowering of blood pressure. Edema and albuminuria were little affected.—*J.M.*

GONADS

DEL CASTILLO, E. B., AND C. GALLI-MAININI

Metrotrophic action of testosterone. *Medicina Buenos Aires. 5:* 144 (1945).

The author reports two cases of dwarfism with infantilism in which menstruation was induced by the administration of testosterone. The actions of sexual steroids on the endometrium are analyzed and the metrotrophic action of testosterone is discussed. The authors conclude that there is a "critical level" in the concentration of the sexual steroids above which

menstruation is inhibited and below which menstruation occurs.—*F.A. de la B.*

HAMAN, J. O.

Exercises in dysmenorrhea. *Am. J. Obst. & Gynec. 49* (6): 755–761 (1945).

The author treated by exercises 129 women who complained of severe dysmenorrhea, 84 of the primary type and 45 of the secondary type. He reported that 84.5 percent of the entire group and 89.3 percent of the primary type group had definite relief. In many instances this lasted for at least 24 months which was the limit of the follow-up.—*C.D.D.*

HARDING, F. E.

The treatment of functional dysmenorrhea with pregneninolone. *Am. J. Obst. & Gynec. 50* (1): 56–63 (1945).

Pregneninolone, in doses varying from five to 15 milligrams orally daily, was administered to 83 patients with functional dysmenorrhea. Treatment was started from the fourteenth to the twenty fourth day and continued until bleeding began or the pain lessened. There was satisfactory improvement (50 percent or better) in 60 patients. There was a tendency for the pregneninolone to cause the bleeding to appear early but this was prevented by starting the treatment late in the cycle. There were no other consistent changes in the menstrual cycle.

Twenty patients were given progesterone, five to 15 milligrams, intramuscularly during the actual time of the severe pain. The results were disappointing as very little relief was obtained.—*C.D.D.*

KARNAKY, K. J.

Possible use of kymographic tracing instead of endometrial biopsy for the determination of ovulation. *West. J. Surg. 53*: 237–243 (1945).

For the speedy determination of the type of contractions occurring in the uterus, the author describes the following technique: a small uterine cannula covered with a small collapsed balloon is inserted through the cervical canal into the uterine cavity. The cannula is attached to a kymographic writing needle by a rubber tube. With the kymograph in operation, the pressure is slowly increased to 80 millimeters of mercury. The tracing obtained after five to 15 minutes will indicate whether the uterine contractions are of the "resting or estrogenic" or of the progesterone type. The test for progesterone waves may be done: (1) Seven to ten days before the expected date of menstruation (2) On any day of menstruation or uterine bleeding (3) One to 3 days after the end of menstruation or uterine bleeding. The accuracy of the method was tested by correlating the tracings with endometrial biopsies in 200 patients. One hundred and seventy-six who gave secretory tracings had secretory endometria. Twenty four had small tracings, called estrogenic or no tracings at all. They all had proliferative endometria with or without dilated glands. Acute vaginitis, cervicitis, endometritis, salpingitis, incomplete abortions, pregnancy and malignancy were considered contraindications to the use of the method. No complications have resulted from 1227 consecutive determinations. The procedure is less painful than endometrial biopsy.—*J.M.*

WEINBERG, C. H.

Essential dysmenorrhea. Its treatment with pavatrine. *Am. J. Obst. & Gynec. 50* (1): 98–101 (1945).

In a series of 100 patients with essential dysmenorrhea, 48 had complete relief and 42 needed in addition only mild sedation when treated with pavatrine. This was given three times daily, beginning three days before the expected period and was continued through the first day of bleeding. This drug possesses both musculotrophic and neurotrophic action but is not a narcotic like morphine, which action it simulates.—*C.D.D.*

THYROID

BARTELS, E. C.

Use of thiouracil in the preoperative preparation of patients with severe hyperthyroidism. *Ann. Int. Med. 22:* 365–372 (1945).

Sixty-four patients with severe hyperthyroidism have been prepared for operation with thiouracil at the Lahey Clinic since the report issued in May 1944. Fifty of these patients had primary hyperthyroidism and 14 had adenomatous goiter with hyperthyroidism. The disease was considered to be severe in these patients because of their being in the older age group, because of the long duration of the disease and high basal metabolic rates. In 15 of the patients, thyrotoxicosis was complicated by auricular fibrillation or cardiac failure. Thiouracil was administered in a daily dosage of 0.6 gm. When the basal metabolic rate approached +20%,

iodine was added and the two drugs given simultaneously for three weeks. The involution effected by iodine was adequate to overcome the technical operative difficulties experienced with the highly vascular glands resulting from therapy with thiouracil alone. Thiouracil was discontinued one week prior to operation. All patients except those in cardiac failure were treated at home and returned to the clinic every two or three weeks for examination and differential white blood counts. Patients in cardiac failure were hospitalized until compensation was restored. Subtotal thyroidectomy was performed in 52 cases and hemithyroidectomy in 12. Patients in whom thiouracil was given long enough to lower the BMR to normal experienced a smooth anesthesia and negligible postoperative thermal response as compared with iodine-treated patients. The records of two patients who were operated upon before thiouracil had lowered the BMR to normal are presented. These patients had such an unsatisfactory operative course that hemithyroidectomy only was performed and despite this precaution severe postoperative reactions occurred. Patients not previously treated with iodine exhibited approximately one per cent decline in the BMR per day of treatment with thiouracil. Out of a grand total of 119 patients treated with thiouracil, eight displayed toxic reactions consisting of: (a) skin eruption, 1; (b) febrile reaction, 4; (c) leukopenia, 3. All of the reactions disappeared on discontinuance of the drug, although one patient was in the early stages of agranulocytic angina. The author concludes that thiouracil is of great value in the preoperative management of patients with severe hyperthyroidism, in that it greatly reduces the risk of surgical treatment.—*J.M.*

BEARDWOOD, J. T., JR., AND D. C. LEVINSON

Thiouracil in the medical management of hyperthyroidism. *Pennsylvania M. J. 48:* 212 (1944).

In 18 of 20 cases of thyrotoxicosis, thiouracil restored the BMR to normal, with clinical remission and weight gain. Maintenance dosage over several months is better than intermittent treatment. An initial dose of 0.6 gm. daily is recommended. Serum cholesterol, urinary creatine determinations and galactose thyroid function tests were made. The action of thiouracil is believed to be specific, interfering directly with the synthesis of thyroxine.—*Courtesy Biol. Absts.*

DOBYNS, B. M.

The influence of thyroidectomy on the prominence of the eyes in the guinea pig and in man. *Surg., Gyn., & Obst. 80:* 526–533 (1945).

Changes in the prominence of the eyes of 233 patients and 13 guinea pigs after thyroidectomy have been studied. The Hurthle exophthalmometer was employed for measuring the eye changes in patients. Two ingenious devices of the author's design, a caliper instrument and a modified camera lucida, were used to make corresponding measurements in the animals. Increase in prominence of the eyes of both patients and experimental animals was found. Patients who had adenomatous goiter with hyperthyroidism or exophthalmic goiter developed a greater increase in prominence post-operatively than did patients who had adenomatous goiter without hyperthyroidism. Patients whose metabolic rates fell only slightly after operation were inclined to relatively slight increase in prominence of the eyes, whereas those whose rates fell markedly showed a relatively greater increase in prominence of the eyes.—*J.M.*

EATON, JAMES C.

Treatment of thyrotoxicosis with thiouracil. *Lancet 248:* 171 (1945).

Thirty-six cases of thyrotoxicosis were treated with thiouracil, twenty-five of which were observed for at least six months. Included were 4 with toxic adenoma, 4 recurring after thyroidectomy, 4 diabetics and 2 during pregnancy. The maximum dose was 800 mg. daily, with 200 mg. as a maintenance dose. Seven cases have remained well after treatment though the drug was not given for periods of three and one-half to eight months. Others had to continue the drug for a year. One case showed granulocytopenia without symptoms which was relieved by cessation of the drug. The thyrotoxicosis was relieved in the pregnant women but one child was born with an enlarged thyroid. Three diabetics in which the diabetes was primary responded well to thiouracil. One in which the hyperthyroidism was primary was the only patient who failed to respond. Exophthalmus was not appreciably affected. The changes in the size of the thyroid were irregular with the mean circumference of the neck showing no significant change. Charts of mean change in BMR, pulse rate, pulse pressure, body weight and white cell count are given.—*L.T.S.*

GOLDSMITH, E. D., A. S. GORDON AND H. A. CHARIPPER

An analysis of the effects of continued thiourea treatment in pregnancy and on the development of the offspring in the rat. *Am. J. Obst. & Gynec. 49:* 197 (1945).

At intervals of 0 to 22 days prior to parturition, pregnant rats were placed on a laboratory stock diet containing 0.5 per cent thiourea. This resulted in activation and hyperplasia of the thyroid gland and retarded growth of the offspring. A return to a normal diet was marked by a return to normal growth and physiological activity. The authors advise caution in the use of thiourea and thiouracil therapy in pregnancy complicated by hyperthyroidism.—*C.D.D.*

HAINES, S. F., AND F. R. KEATING, JR.

Unusual reactions following the use of thiouracil. *J. Lab. & Clin. Med. 30:* 354 (1945).

Two individuals developed unusual reactions to thiouracil which the authors attributed to a "toxic disturbance of the central nervous system." Both patients were confused, somnolent and developed myoclonic contractures of various muscles. After complete subsidence, this unusual response was reproduced in each instance, by resumption of the drug. However, one of the two patients had a similar reaction to the "administration of an inert substance." Therefore the nature of the reaction in association with thiouracil therapy still remains in doubt.—*T.H.McG.*

HOUSSAY, B. A.

Thyroid and diabetes. *Semana méd. Tomo Cincuentenario. 1:* 255(1944).

Many of the effects of the thyroid on carbohydrate metabolism have no relationship with the pancreas. In hyperthyroidism the blood sugar curve is often high and prolonged after ingestion of glucose and almost invariably after galactose. During the period of absorption, the respiratory quotient is high. The fasting blood sugar in hyperthyroidism is normal, but there is a sharp rise after breakfast and often a slight glycosuria. Experimental hyperthyroidism causes a decrease of hepatic glycogen, also a diminution of cardiac glycogen. That of the muscle is more resistant. The glycogen is not changed in hypothyroidism or only slightly reduced except in advanced states of insufficiency or cachexia, when it decreases markedly. The glycogen mobilization is diminished during the action of insulin or adrenalin. The acidosis inherent to hyperthyroidism may produce histological lesions in liver and heart. The sensitivity to insulin is augmented in hypothyroidism with slow recovery from hypoglycemia and danger of convulsions and death in shock. In hyperthyroidism, the sensitivity to insulin is generally lowered except for the stages of depletion of glycogen. Coexisting hyperthyroidism and diabetes aggravate each other mutually. The excess of thyroid hormone may have directly a damaging effect on the islands of Langerhans. Thyroid feeding has not produced diabetes in animals with intact pancreas. If the pancreas is reduced in size by operation or damaged with pituitary extract, thyroid feeding will cause diabetes with polyuria and acidosis. This effect, reversible at the beginning, becomes permanent with prolonged medication. The resulting diabetes is called metathyroid diabetes. While hyperthyroidism is not more frequent among diabetics than in the general population, the incidence of diabetes is markedly higher among hyperthyroid patients. In patients having both ailments simultaneously immediate and ample thyroidectomy is imperative. The diabetogenic action of the thyroid is weaker than that of the pituitary. Thyroidectomy does not improve the diabetes in pancreatectomized dogs. In human diabetics, total thyroidectomy causes a slight increase in carbohydrate tolerance and a reduction in insulin requirements. However, the myxedema thus produced is a disadvantage that far outweighs the slight improvement in the diabetic state.—*A.E.M.*

HURXTHAL, L. M.

Experiences with the use of desiccated thyroid. Methods of detecting self-induced hyperthyroidism, with a report of a case in which auricular fibrillation occurred. *N. Y. State J. M. 44:* 2217 (1945).

Heart pain in myxedema may occur at different times and under different circumstances. It may begin with the onset of myxedema and may be relieved as treatment progresses. On the other hand, it may increase with routine treatment and may occur even with small doses of thyroid in some patients. Anginal pain is unusual before treatment. Coronary infarction or prolonged anginal seizures may occur at onset of treatment, when dose is increased or when patient appears to be stabilized. In general, the younger the patient, and the shorter the duration of the disease, the less chance there is of the

development of angina pectoris. A young patient with angina before treatment is likely to obtain relief with treatment. The dose is reduced on appearance of sternal or precordial pain and continued at that level for one or two months. All thyroid should be discontinued for several weeks following anginal seizure or coronary infarction. In panhypopituitarism, secondary myxedema and pituitary hypoadrenalism may be present. In these cases, thyroid may be poorly tolerated and may precipitate an acute adrenal insufficiency. The use of desiccated thyroid when not specifically indicated has several dangers. Ordinary doses may not have a serious effect on the heart of a patient without myxedema unless coronary insufficiency is present. Larger doses may activate a latent diabetes. Exophthalmic goiter has been reported following the use of thyroid for weight reduction. Patients may take thyroid secretly for weight reduction or as a source of energy or mental stimulation. This possibility should be suspected in patients who have clinical evidences of hyperthyroidism with a normal thyroid gland on palpation. It should be considered in patients who have had a subtotal thyroidectomy and who continue to be thyrotoxic without recurrent or persistent hyperplastic remnants. The basal metabolic rate is high and iodine is found in large amounts in the urine and in the blood. With the exception of exophthalmos and an abnormal gland, induced hyperthyroidism is indistinguishable from the true hyperthyroidism and considerable detective work is sometimes necessary to establish thyroid addiction.—*M.B.G.*

PALMER, E. V.

Hyperthyroidism and thiouracil. *Ann. Int. Med. 22:* 325–364 (1945).

Fifty unselected cases of thyrotoxicosis have been treated with thiouracil at the University Hospital in Baltimore for varying periods up to ten months. In 42 of the cases the management has been exclusively medical. Thyroidectomy was performed in eight cases for cosmetic reasons or because the patient was unable to return weekly for laboratory studies. Thiouracil was administered in a dosage of 0.1 gm. every three hours for three days; 0.1 gm. every four hours for three to six days and then 0.4–0.5 gm. daily until sustained clinical improvement was observed. A maintenance dosage of 0.1–0.3 gm. daily was usually arrived at within three months. Adjunctive therapy in cases most recently treated consists of sodium bicarbonate with each dose of thiouracil, cevitamic acid, liver extract, multi-vitamin concentrates and either thyroxin or desiccated thyroid. Patients were hospitalized until the basal metabolic rate had undergone a sustained fall. No case failed to respond to thiouracil although some responded more satisfactorily than others. Four cases receiving exclusively medical management have now been off thiouracil for three months and have so far experienced no recurrence of thyrotoxic symptoms. Patients relapsing because thiouracil was discontinued too soon or because of intercurrent infection or emotional stress have responded as satisfactorily to a second course of thiouracil therapy as the first. In the author's opinion, the administration of thyroxin or desiccated thyroid did not impede the response to thiouracil and had the following advantageous features: (1) increase in subjective well-being; (2) prevention of pitting edema; (3) prevention of ocular irritation in patients with exophthalmos; (4) prevention of the enlargement of the gland produced by thiouracil therapy. Toxic reactions comprised: (1) nine cases of transient leukopenia; (2) three cases of microscopic hematuria and crystalluria; (3) one case of classical pityriasis rosea, probably unrelated to thiouracil. The author suggests that the thiouracil effect is brought about by depression of normal enzyme reactions of tissues in general but especially the pituitary (leading to suppression of synthesis of thyroid stimulating hormone) and of the thyroid (leading to inhibition of iodine uptake).—*J.M.*

SCHWARTZ, A. R.

Exophthalmic goiter in children. *Arch. Ped. 62:* 214 (1945).

The author reports the case of an infant aged two years and three months who developed classical signs of exophthalmic goiter including exophthalmos, nervousness and restlessness, failure to gain weight, excessive perspiration, flushing of skin, enlargement of the thyroid gland, tachycardia, and low serum cholesterol. Because of the child's age and the severity of the disease she was given x-radiation to the thyroid gland. This caused an improvement in her condition for seven months and then the manifestations recurred in an exaggerated form. At this time a bilateral thyroidectomy was performed, following which the patient had an acute exacerbation of the thyrotoxicosis and died one hour post-operatively. The removed

gland showed extremely marked papillary hyperplasia of the thyroid with lymphoid infiltration. A post-mortem was not performed. The author reviews the literature and points out that although this condition is extremely rare in children it does occur and therefore should be borne in mind.—*E.C.R., Jr.*

THOMPSON, W. O., AND P. K. THOMPSON

Changes in the treatment of toxic goiter produced by thiouracil. *J. Lab. & Clin. Med.* 30: 354 (1945).

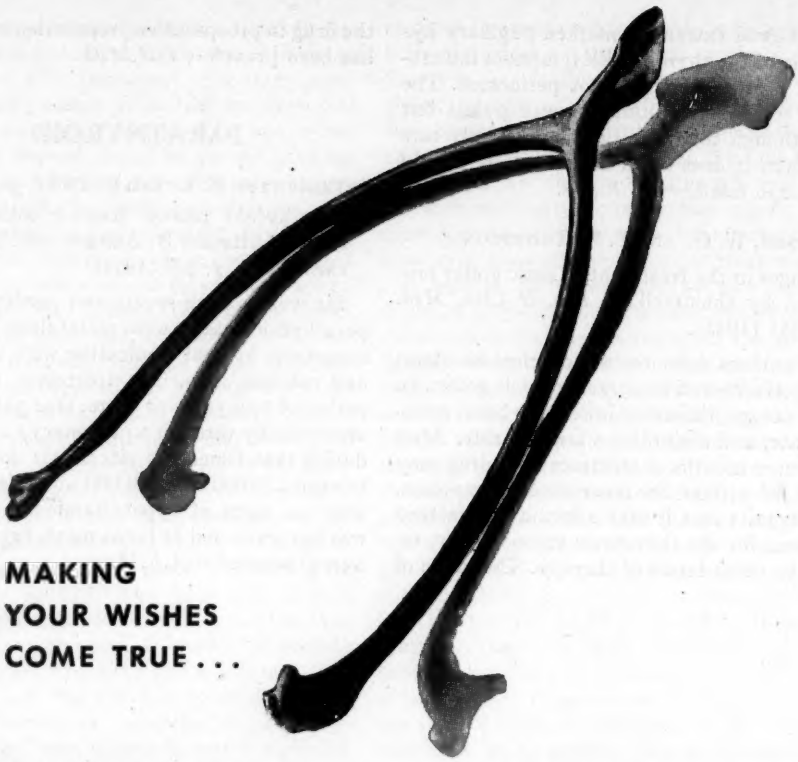
The authors draw certain conclusions about the effectiveness of thiouracil in toxic goiter. In proper dosage, thiouracil lowers the basal metabolic rate, and maintains a lowered rate. After six or more months of treatment the drug may be omitted without the recurrence of ymptoms. This suggests that it may afford a satisfactory treatment for the thyrotoxic state without recourse to other forms of therapy. The value of the drug in preoperative preparation of patients has been proven.—*T.H.McG.*

PARATHYROID

SEVRINGHAUS, E. L. AND RUTH ST. JOHN

Parathyroid tetany treated with massive doses of vitamin D. *Semana méd. Tomo Cincuentenario, 1:* 327 (1944).

Six women with severe and persisting hypoparathyroid tetany were maintained free from symptoms by oral medication with vitamin D and calcium salts. The treatment covered a period of two years or more. One patient went uneventfully through a pregnancy and delivery during that time. The vitamin D doses varied beween 150,000 and 400,000 units daily. There were no signs of hypervitaminosis. The diet was not restricted as far as meat, eggs and milk were concerned.—*A.E.M.*



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